Updating the therapeutic strategy in RA What is effective, what is changing in daily practice regarding the use of DMARDs and biological agents in the Balkan countries

The Greek experience

(THE CHANGING LANDSCAPE)

Spyros Aslanidis, MD

Hippokration GH, Thessaloniki, Greece

DISCLOSURES

No conflict of interest for the present talk

Consultation fees and honoraria in the last two years:

ABBVIE, Actelion, MSD, Roche, UCB

RA PREVALENCE IN GREECE

- **0.67%**
  - **Around 70,000 patients**
    - **ESORDIG study, J Rheumatol, 2003**

- **No official data exist regarding their therapeutic regimens**

What is in effect

THERAPEUTIC PROTOCOLS EXIST
BY THE GREEK NATIONAL DRUG ORGANIZATION (EOF)

- Not compulsory
  - Ongoing changes
- More “setting the frame” rather than stepwise
  - Provide general guidance
- Characterized as “too short” by officials

National therapeutic protocol for RA prescription

Therapeutic targets

Basic treatment principles (T2T)

- Treatment goal **is remission or LDA** as soon as possible (3-6 months)
- If the goal is not achieved, therapy must be **adapted** according to disease activity with frequent and tight follow-up every 1-3 months
- Treatment with **DMARDs** must start as soon as the disease is diagnosed
- If therapy with the 1st DMARD does **not achieve** the target and poor **prognostic factors** exist, a **biologic agent** must be added
- If there are **no** poor prognostic factors, **add or switch** to another DMARD (leflunomide, cyclosporine, sulphasalazine, gold, hydroxychloroquine)

Poor prognostic factors

- Presence of RF and/or anti CCP ab, especially in high titers
- Presence of bone erosions in hand or feet xrays
- High disease activity (based on indices of disease activity, number of swolen joints or acute phase reactants)

National therapeutic protocol for RA prescription (cont.)

1st treatment choice

- **Corticosteriod 7.5mg/d + MTX (7.5 – 20 mg/wk, max 25 mg/wk) + folic acid (5mg/wk)**

- **In case of MTX intolerance the following can be used instead (monotherapy or combinations): leflunomide, cyclosporine, sulphasalazine, gold, hydroxychloroquine**

- **Duration of treatment at least 3-6 mo**
  - **Response to treatment must be assessed in 3-6 months. Continue treatment only if there is adequate response**

What is in effect

DMARDs

- **DMARDs**
  - **75% reimbursement (vs 100% previously)**
- **Rheumatologists seem to continue DMARD therapy for longer periods ?**
- **? Bibliographic data**
  - **SWEFOT (Lancet 2012), TEAR (A&R 2012)**
- **? Emerging difficulties in prescribing biologics**

National therapeutic protocol for RA prescription (cont.)

2nd choice

In cases of 1st treatment choice failure with poor prognostic factors (keeping in mind differences in cost) add

- **anti-TNF agent (infliximab, adalimumab, etanercept, certolizumab, golimumab) *or***
- **one of the following: Abatacept, Anakinra (not recommended by the committee),Tocilizumab**
  - ***Always consider coexisting diseases, eg HBsAg positivity***

-3rd choice

- **In cases of 2nd choice treatment failure or toxicity switch to another biologic agent, anti TNF, abatacept, rituximab, tocilizumab**

National therapeutic protocol for RA prescription (cont.)

Comments

- Comorbidities must be taken into account before making a biologic treatment choice.
- Biologic treatment in RA must be administered in combination with MTX and should be continued only if good clinical response is achieved. If not, the biologic agent should be changed or any other intervention to treatment should be made
- The treatment must be cost effective for the patient

➢ *No use of specific disease activity measurements (i.e. DAS28, SDAI) is proposed / specified in the national protocol, though most physicians do use DAS28 to evaluate disease activity.*

What is in effect

THERAPEUTIC RECOMMENDATIONS

(GREEK SOCIETY OF RHEUMATOLOGY, UPDATED 2012)

- **MORE DETAILED**

- **Refer to the use of DAS 28 as means of establishing active disease**
- **Make the distinction between established and early disease**
- **Recommend initiation of antiTNF drugs**
  - **In active disease DAS>5.1**
  - **In DAS>3.2 and coexistence 2 factors of poor prognosis**
  - **AND failure of >1 or >2 DMARDs, depending on existence of PPF**
- **Specify adequate dosing of DMARDs before failure is decided**

What is in effect (cont)

THERAPEUTIC RECOMMENDATIONS

(GREEK SOCIETY OF RHEUMATOLOGY, UPDATED 2012)

- **Recommend use of DMARD combination, or combination of DMARD with antiTNF drugs in early RA**
  - **In active disease (DAS>5.1 or >6 swolen and >6 tender joints)**
  - **AND presence of > 2 factors of poor prognosis**
- **Recommend follow up of patients using specific activity indices (eg DAS28)**
- **Recommend switching to a 2nd anti TNF or using abatacept-rituximab-tocilizumab**
  - **Specific reference is made to anakinra, which is cosidered less effective than antiTNF agents and is not recommended as a first biologic**

Common practice

- Tight Control / Treat to Target: is more and more accepted by physicians
  - ? not easy to follow; not all patients are able to return to the clinic within 3 months
- I.V. administration is becoming more and more difficult in public hospitals
- Naïve / switch patients
  - was 50%-50%,
  - current trend is towards switching 30%-70%
- Treatment strategy (initiation, switching, withdrawal) lies on treating physician’s judgment

Screening before treatment initiation (common practice)

1. TB screening/prophylaxis

- PPD test
- Chest x-ray

Patient with positive PPD (>5mm) and negative x-ray has to be administered 6 month prophylaxis treatment. 1 month after prophylaxis treatment initiation the physician can start the biologic therapy. Afterwards prophylaxis and biologic treatment administered together until the 6th month.

- In patients with strong suspicion of TB besides a negative PPD test, Quantiferon test can be performed. If the test comes positive the patient receives prophylaxis treatment for 6 months

2. Screening for hepatitis infection

Who actually receives biologics

- **No official numbers exist**

Biologic treatment disposition

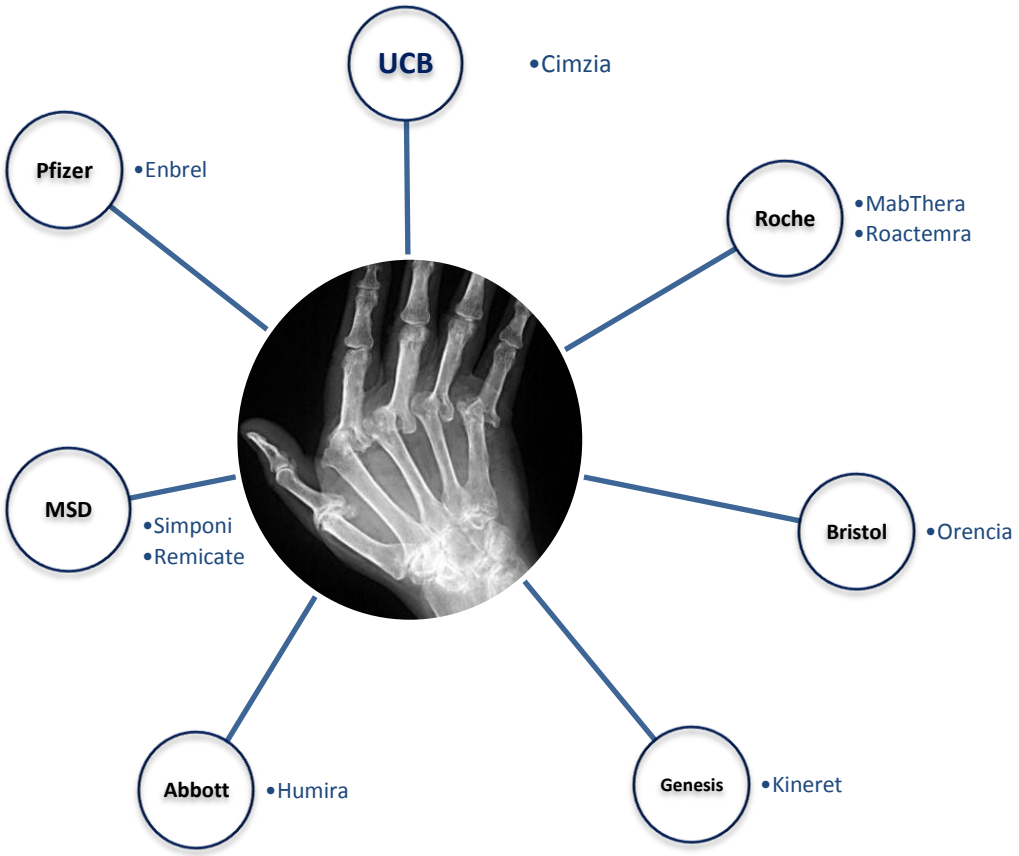
- **HCP is obliged to document that his/her patient suffers from moderate to severe RA that does not respond to standard treatment**
  - ***there is no requirement yet from the local authorities to state disease activity by providing DAS28 measurement*.**

- **Eligible patients in order to have their prescription dispensed by the pharmacist they are obliged to obtain and present an OFFICIAL MEDICAL REPORT**
  - **from a state or private hospital or institution which is adequately equipped**
  - **? SPECIALTY**

- **Patients receive their drug from from central pharmacy**
  - **EOPYY is the biggest public sick fund in Greece**
  - **Currently EOPPY most of insured citizen with the intention to cover the 100% of Greek insured patients and Hospital pharmacies**

- **Reimbursement coverage 100%**

Biologic Therapies of RA, *7 Companies, 9 products*



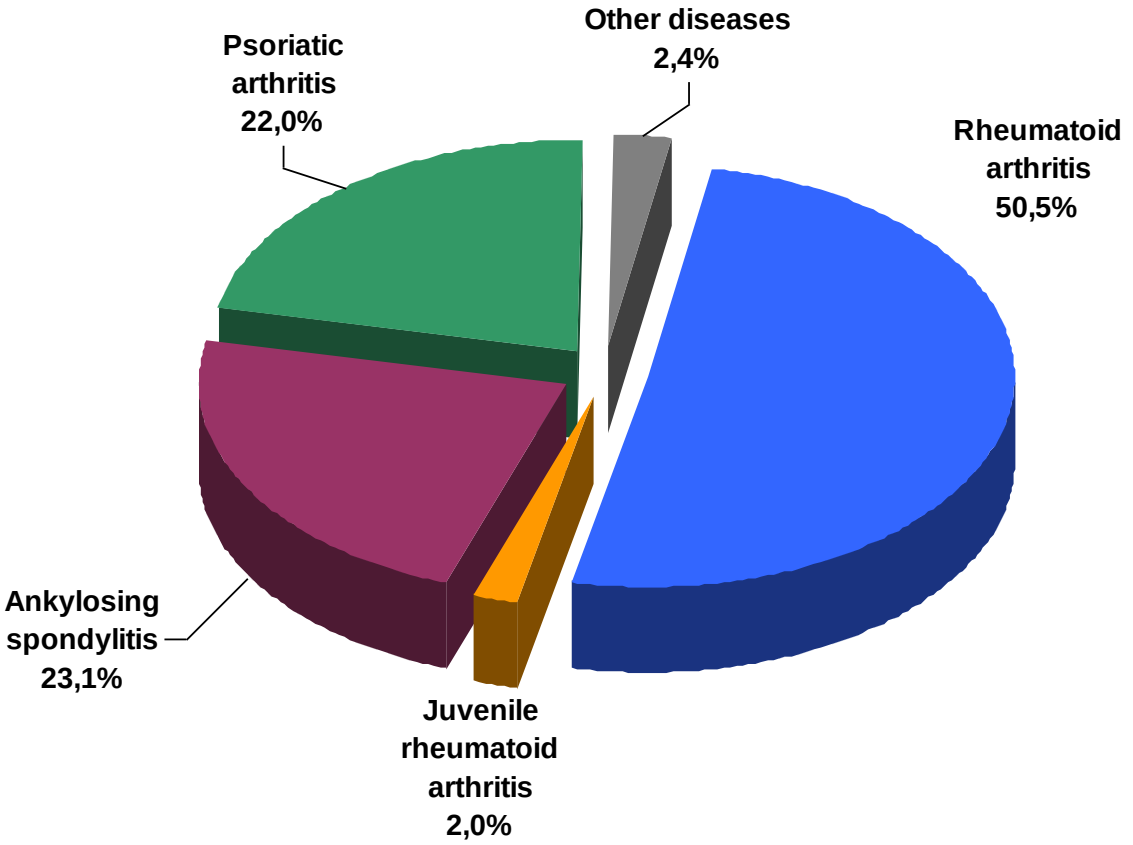
- ✓ Estimated size of market ~100 mil euros
- ✓ Market in mature phase
- ✓ First introduction of anti TNF in 2000 (Infliximab).
- ✓ Applied therapeutic protocol follows EULAR Guidelines
- ✓ 0% co –payment for patients treated with biologics

Diseases Patients Share regarding BRM treatments

no official number -estimate 11-14K pts

The estimated total number of patients treated with BRMs is 28,000-29,000.

50% of these patients concern rheumatoid arthritis.



% refer patients

Source: Cegedim

Questions that arise

- **Official medical record compulsory**
  - **No problems with DMARD prescription**
  - **No problem with biologics (provided that an official medical report exists)**
    - **Initial treatment**
    - **Continuation of treatment**
    - **? WHO ISSUES THE OMD**

- **Biologics supplied cenrally**
  - **EOPPY pharmacies**

Problems in biologic drug prescribing

- Central supply from EOPYY for biologics
  - SC biologics
    - Specific categories of insured patients get them from hospital pharmacies
  - IVGenerally not provided by the hospital pharmacies
    - Only for specific cases
  - Delays fulfilling prescriptions are becoming common

European Pharmaceutical Market

Development trend (2001-2015)

2001-2005

Regions	CAGR
Europe	**8%**
Top 5	7%
Other West	8%
Eastern	13%
Greece	**19%**

2006-2010

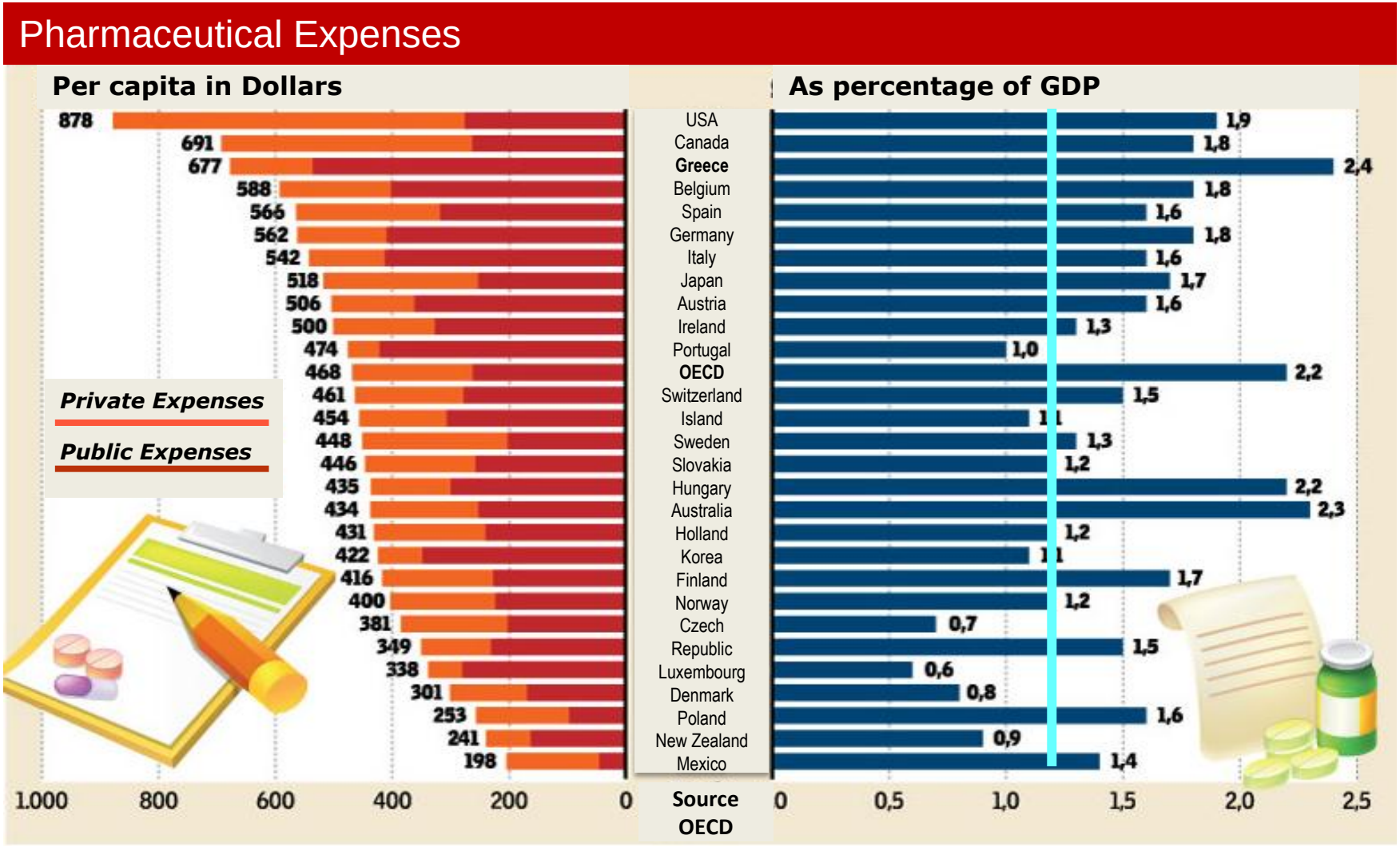
Regions	CAGR
Europe	**6%**
Top 5	5%
Other West	4%
Eastern	11%
Greece	**7%**

2011-2015 forecast

Regions	CAGR
Europe	**1-4%**
Top 5	0 - 3%
Other West	(-1) - 2%
Eastern	6-9%
Greece	**(-3)-0%**

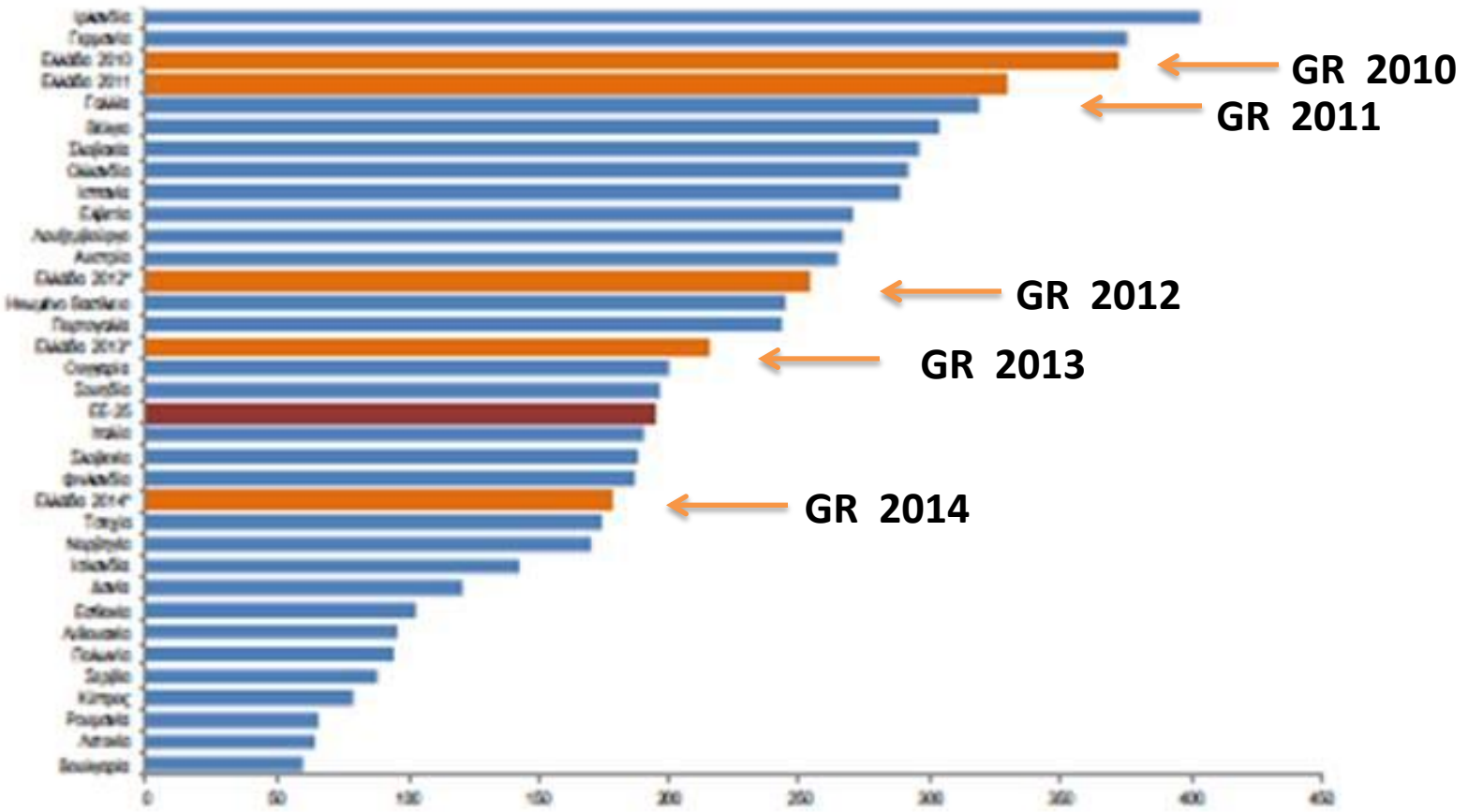
Source: IMS Market Prognosis, October 2011 Note includes EU and non-EU countries.

2009 Pharmaceutical Expenses in Greece as GDP %



2012 Target:1,2

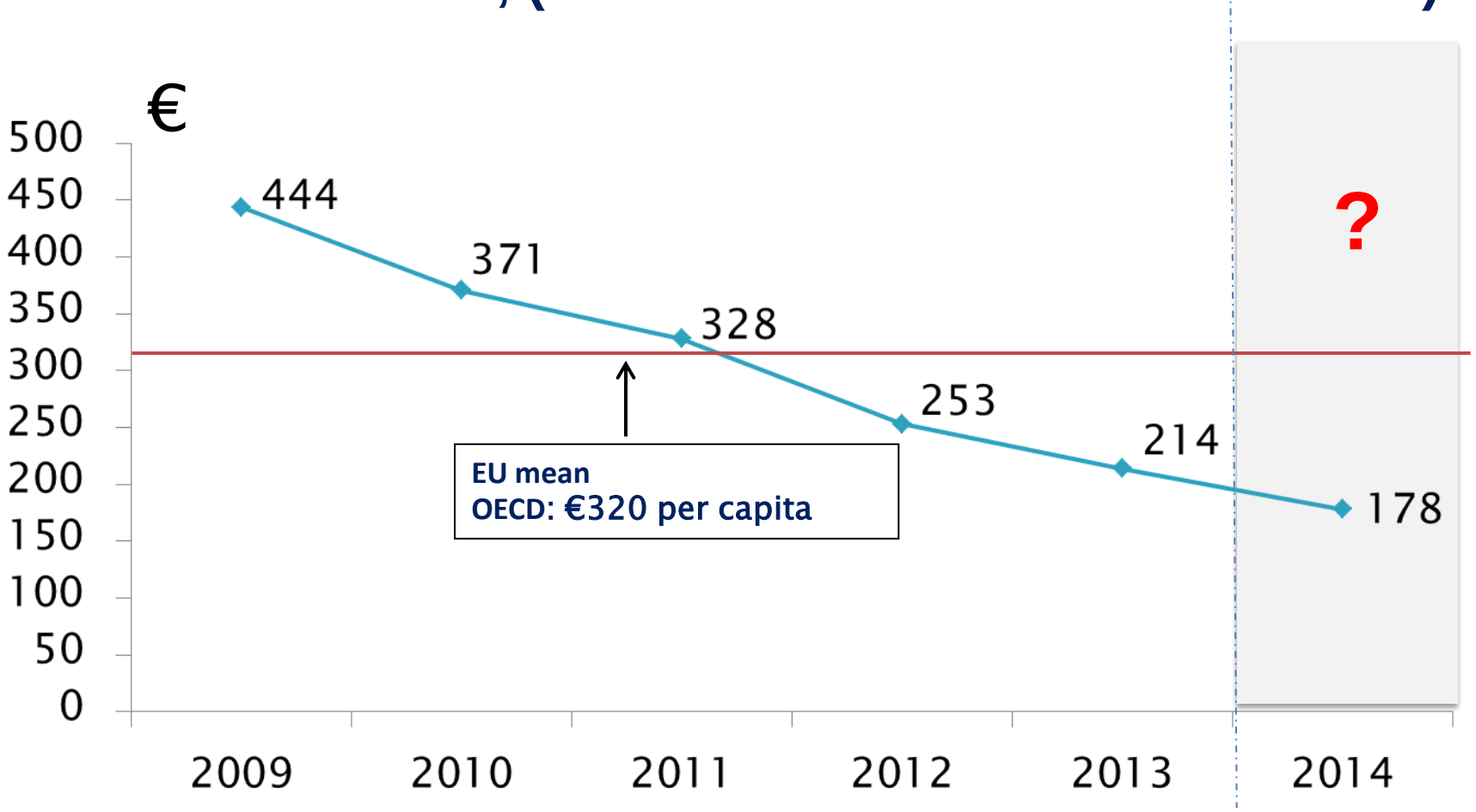
Pharmaceutical expences per capita, EU



Source: OECD, Health Data 2012 (prices derived from IOBE institute)

REDUCTION OF PHARMACEUTICAL SPENDING PER CAPITA, GREECE

2013 vs 2009: 52%, (33% lower than EU mean for 2014)



Source: IOBE/SfEE, Facts & Figures 2012

Market Access Challenges for Rx Biologics

- **Government implements new policies in health issues**
- **Sick funds are struggling to cover pharmaceutical expenditures and asks physicians to prescribe less expensive drugs**
- **Ministry of Health changes reimbursement policy for chronic diseases**
- **Stricter control of prescribing budget/doctor**
  - **introduction of electronic prescribing**
  - **Compulsory use of generic drugs**
- **Continuous cuts on drug prices**
- **Patients visiting private doctors are turning to public hospitals due to financial crisis**