Drug information by public health institutions: results of an 8-country survey in Europe

Giulio Formoso
Emilia-Romagna Region (Italy)
International Society of Drug Bulletins (ISDB)

EMA – March 8, 2016

Evidence-based drug information and its substandard translation into clinical practice

- The overflow of information in print and through the internet often lacks **quality** (**validity**, **generalizability** …)
- … and often does not address **information needs** of physicians, patients and citizens at large
- Selecting valid and relevant information and improving its access as well as uptake may be even more important in an era of accelerated approvals

International Society of Drug Bulletins (ISDB)

- Independent drug information bulletins, in particular those associated with the International Society of Drug Bulletins (ISDB) have partly filled the gap in providing evidence-based, independent information …

- … to help physicians and decision makers assess the added therapeutic value (ATV) of medicines and translate data from scientific literature into possible choices for clinical practice

Some examples of ISDB bulletins

Prescire.org

THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

dtb

Drug and Therapeutics Bulletin

THE INDEPENDENT REVIEW OF MEDICAL TREATMENT

Our qualitative survey

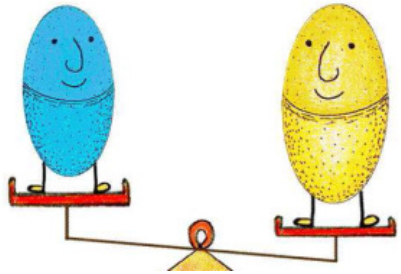
Between April and July 2015 we carried out a survey asking editors of 8 ISDB bulletins of the European region (one per country) to indicate:

- the main sources of drug information, targeted at health professionals and at the general public, provided by National Competent Authorities in their countries
- the specific kinds of information produced
- their opinions about **strengths and weaknesses** of such information and their **suggestions** about how to improve access to good quality information

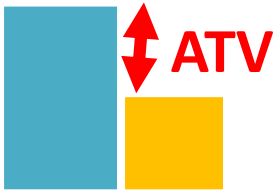
Our qualitative survey

We particularly considered the presence of information on

- **comparative** effectiveness and safety



- the added therapeutic value (**ATV**) of drugs



- assessment of **quality** of scientific evidence

- "**implementability**" of information

8 countries analysed

Austria, Czech Republic, France, Germany, Italy, Netherlands, Spain, United Kingdom

Availability of key information from regulatory authorities and public health institutions in the surveyed countries

Countries	Assessment of added therapeutic value (ATV)	Assessment of quality of scientific evidence
Austria	No	No
Czech R	No	No
France	Evidence-based reports by HAS Transparency Committee provide explicit comments on ATV (amelioration du service medical rendu)	Some information in evidence-based reports from HAS
Germany	Transparent evaluation by the Federal Joint Committee (G-BA) using IQWiG dossier, pharmaceutical company dossier and hearings (with the participation of patients' representatives and professional medical societies)	High quality information in IQWIG reports
Italy	No	No
Netherlands	Some information in pharmacotherapeutic reports of the National Health Care Institute	No
Spain	Some information from AEMPS drug assessment reports	Some information in AEMPS drug assessment reports and in guidelines (GuiaSalud)
UK	Transparent evaluation from NICE reports of ATV from both the clinical and societal standpoint	High quality information in NICE reports and guidelines

Examples from UK: technical information from NICE

Guidance

NICE National Institute for Health and Care Excellence

4 Consideration of the evidence

Clinical effectiveness

Clinical effectiveness

4.2 The Committee considered the clinical-effectiveness data from ENGAGE AF-TIMI 48, that compared edoxaban with warfarin. It considered that this trial was of good quality and discussed whether the results were generalisable to people with atrial fibrillation in the UK. The Committee noted that ENGAGE AF-TIMI 48 , like other trials of newer anticoagulants, used $CHADS_2$ to assess the risk of stroke rather than $CHADS_2$-VASc, which is now used in clinical practice, as recommended in the NICE guideline on managing $CHADS_2$-VASc scoring TECHNICAL LANGUAGE rom the clinical expert that the who would benefit from anticoagulation because a number people with a $CHADS_2$ score of 1 would still benefit. It also heard that although these people were not included in ENGAGE AF-TIMI 48, a lower baseline risk of stroke would not be expected to reduce the relative efficacy of the treatment. In clinical practice, edoxaban is expected to be offered in the same place in the treatment pathway as other anticoagulants (that is, to women with a $CHADS_2$-VASc score of 2 and above, and to men with a score of 1 or above), while taking bleeding risk into account. The Committee concluded that the trial was well designed and generalisable to clinical practice.

4.3 The Committee considered the results of ENGAGE AF-TIMI 48. It noted that the primary efficacy outcome was a composite of stroke (both ischaemic and haemorrhagic) and systemic embolism.

Examples from UK: information for patients

Examples from UK: information for patients

Frequently Asked Questions ↓	Warfarin	Apixaban	Dabigatran	Rivaroxaban
What do I have to do?	Take warfarin once a day, and have a blood test before you start to make sure it is safe for you.	Take apixaban twice a day, and have a blood test before you start to make sure it is safe for you.	Take dabigatran twice a day, and have a blood test before you start to make sure it is safe for you.	Take rivaroxaban once a day with food, and have a blood test before you start to make sure it is safe for you.
Will it reduce my risk of having a stroke?	With good control of warfarin, 16 in every 1000 patients (1.6%) will have a stroke.	If taken regularly without missing doses, 13 in every 1000 patients on apixaban (1.3%) will have a stroke.	If taken regularly without missing doses, 11 in every 1000 patients on dabigatran (1.1%) will have a stroke.	If taken regularly without missing doses, 17 in every 1000 patients on rivaroxaban (1.7%) will have a stroke.
What is the risk of serious bleeding?	About 36 in every 1000 patients (3.6%) will experience a serious bleed.	About 21 in every 1000 patients (2.1%) will experience a serious bleed.	About 30 in every 1000 patients (3%) will experience a serious bleed.	About 36 in every 1000 patients (3.6%) will experience a serious bleed.
Can the effect be reversed if I am bleeding?	Yes. Treatment can reverse the effects of warfarin in 20 minutes.	No, the effect cannot be reversed.	No, the effect cannot be reversed.	No, the effect cannot be reversed.
What are the other main side effects of taking this medication?	The most common side effects are bleeding, bruising and nose bleeds.	The most common side effects are bleeding, bruising and nose bleeds.	The most common side effects are bleeding, bruising and nose bleeds.	The most common side effects are bleeding, bruising and nose bleeds.
Does this medication need to be closely monitored?	Yes. You will need 8 to 9 blood tests every year to check clotting. Some people need more frequent blood tests.	No. You will need blood tests once or twice a year.	No. You will need blood tests once or twice a year.	No. You will need blood tests once or twice a year.
Are there foods or medicines I should avoid?	Yes. Warfarin is affected by many medicines, food and alcohol.	Yes, but not as many as with warfarin.	Yes, but not as many as with warfarin.	Yes, but not as many as with warfarin.

Examples from Germany: technical information from IQWIG

IQWiG Institute for Quality and Efficiency in Health Care

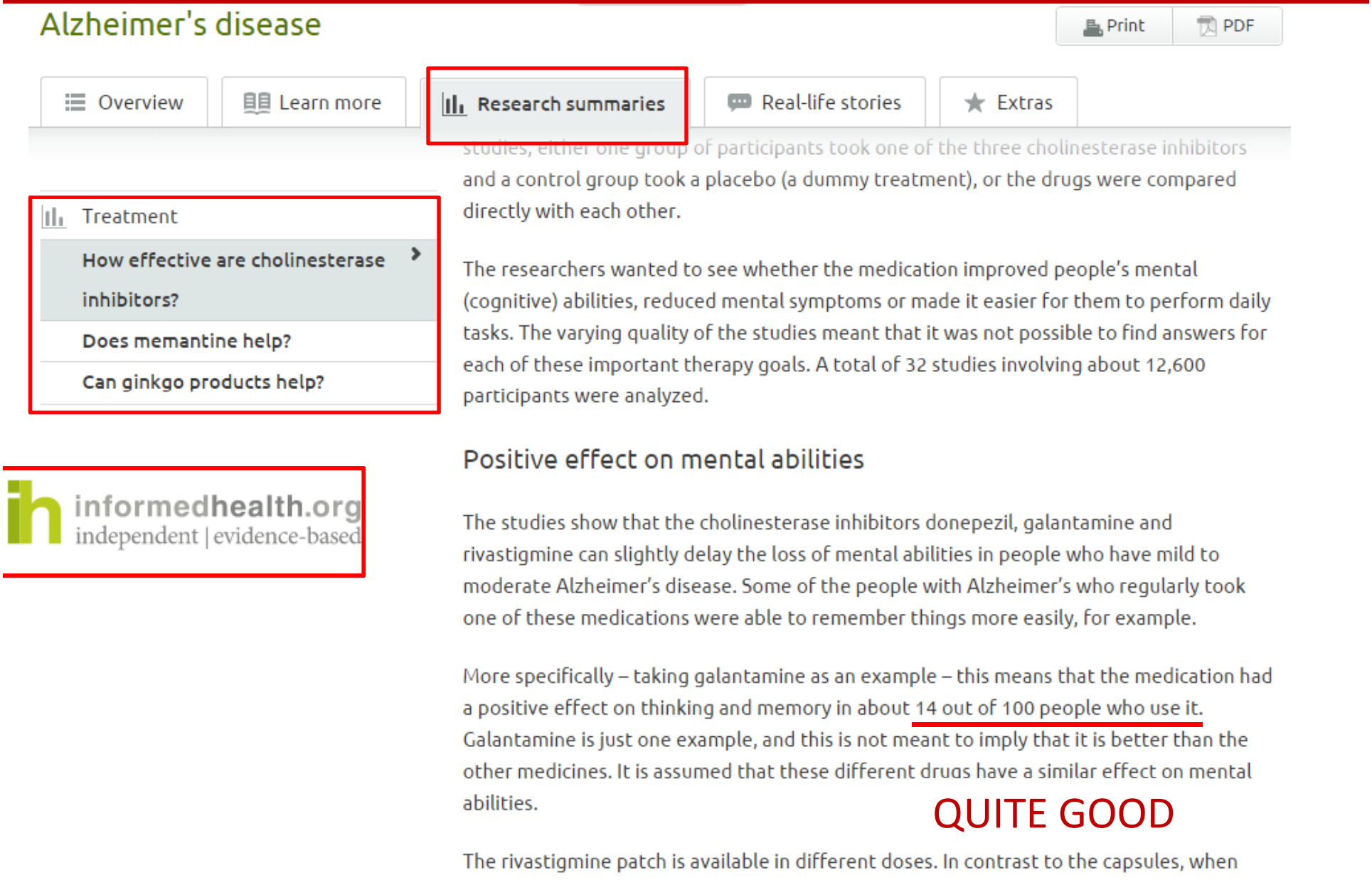
IQWiG Reports – Commission No. A15-29

Edoxaban –
Benefit assessment according to §35a Social Code Book V[1]

Examples from Germany: technical information from IQWIG

Study Outcome category Outcome	Edoxaban N	Edoxaban Patients with event n (%) Event rate (%/year)[a]	Warfarin N	Warfarin Patients with event n (%) Event rate (%/year)[a]	Edoxaban vs. warfarin HR[b] [95% CI]; p-value
ENGAGE AF-TIMI 48					
Mortality					
All-cause mortality	7035	TECHNICAL LANGUAGE			0.92 [0.83; 1.01]; 0.082
Morbidity					
Stroke (ischaemic, haemorrhagic or unknown cause)	7035	281 (4.0) (1.5)	7036	317 (4.5) (1.7)	0.88 [0.75; 1.03]; 0.112

Examples from Germany: information for patients



Alzheimer's disease

Print PDF

Overview | Learn more | Research summaries | Real-life stories | Extras

studies, either one group of participants took one of the three cholinesterase inhibitors and a control group took a placebo (a dummy treatment), or the drugs were compared directly with each other.

Treatment

- How effective are cholinesterase inhibitors?
- Does memantine help?
- Can ginkgo products help?

The researchers wanted to see whether the medication improved people's mental (cognitive) abilities, reduced mental symptoms or made it easier for them to perform daily tasks. The varying quality of the studies meant that it was not possible to find answers for each of these important therapy goals. A total of 32 studies involving about 12,600 participants were analyzed.

informedhealth.org
independent | evidence-based

Positive effect on mental abilities

The studies show that the cholinesterase inhibitors donepezil, galantamine and rivastigmine can slightly delay the loss of mental abilities in people who have mild to moderate Alzheimer's disease. Some of the people with Alzheimer's who regularly took one of these medications were able to remember things more easily, for example.

More specifically – taking galantamine as an example – this means that the medication had a positive effect on thinking and memory in about 14 out of 100 people who use it. Galantamine is just one example, and this is not meant to imply that it is better than the other medicines. It is assumed that these different drugs have a similar effect on mental abilities.

QUITE GOOD

The rivastigmine patch is available in different doses. In contrast to the capsules, when

Problematic traits in many of the countries (about info targeted to either professionals or patients)

- The link between **evidence** and conclusions about effectiveness and safety of medicines is often not clearly shown
- Limits in comparative evidence on efficacy/effectiveness and safety of medicines to show their **ATV** over an appropriate comparator treatment
- Limited **transparency** in the process of selecting the evidence, appraising its quality and showing possible conflicts of interest
- Lack of **primary data from pharmacovigilance**
- Limited "**implementability**" of the available information and lack of plans to actually implement it

How to enhance information transfer?

Highlighting **applicability** and **relevance** of data by sharply describing characteristics of studies

Populations	Are they similar to those we're thinking of (to whom we'd like to transfer results)?
Intervention	Are doses and administration similar to usual practice?
Control	Are doses and administration similar to usual practice?
Outcomes	Are they relevant? and valid?
Time	Is duration of studies consistent with clinical practice?

How to enhance information transfer?

Highlighting **applicability** and **relevance** of data by sharply describing characteristics of studies

Making data more comprehensible by using **absolute risk** differences and NNTs

Populations	Are they similar to those we're thinking of (to whom we'd like to transfer results)?

How to enhance information transfer?

Highlighting **applicability** and **relevance** of data by sharply describing characteristics of studies

Making data more comprehensible by using **absolute risk** differences and NNTs

Showing what the information does add in defining the **place in therapy** of medicines;

Populations	Are they similar to those we're thinking of (to whom we'd like to transfer results)?

How to enhance information transfer?

Highlighting **applicability** and **relevance** of data by sharply describing characteristics of studies

Making data more comprehensible by using **absolute risk** differences and NNTs

Showing what the information does add in defining the **place in therapy** of medicines;

Expliciting where the information comes from and its possible **pitfalls** (publication bias, conflicts of interests)

Populations	Are they similar to those we're thinking of (to whom we'd like to transfer results)?

Different tools for different readers (but diffusion and implementation are different concepts)

Wider spectrum: **from easier to more articulated materials**, specifically targeted (to either professionals or patients) and widely diffused also through **social media**

On webpages or PDFs, use of **hypertexts** for different layers of information, depending on readers' interest in more or less depth, would be of great help

However, **implementation frameworks** would need to be thought of both at national and local level (for example, small group interactive meetings)

Defining therapeutic role and ATV: whose job?

- Should regulatory authorities also offer clear info materials on ATV of drugs (with comparative evaluation of drug effectiveness and safety)?
- Or should regulatory and information functions be separated?
- No question that regulators should be fully transparent about data and reasons informing their regulatory decisions, which are often coupled with reimbursement decisions and inherently linked to an evaluation of ATV
- The availability of such information materials per se is a fundamental issue, whether they are produced by medicines regulatory agencies or by other public health institutions without regulatory functions (like it also happens in UK, Germany or France, just to make some examples).

More information tools at European level?

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

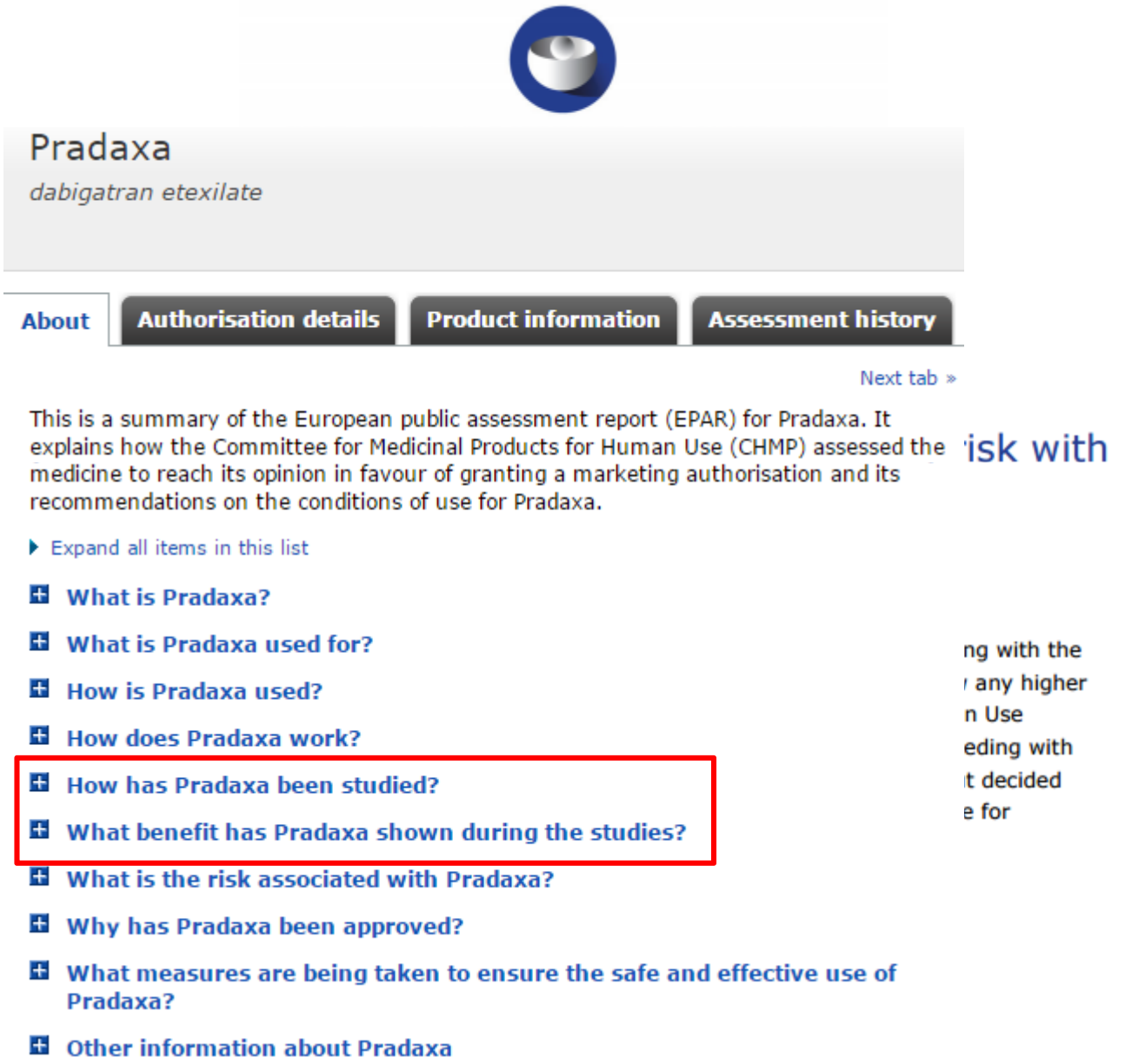
24 May 2012
EMA/CHMP/333240/2012
EMEA/H/C/000829/II/0031

Questions and answers on the review of bleeding risk with Pradaxa (dabigatran etexilate)

On 24 May 2012, the European Medicines Agency completed a review of the risk of bleeding with the anticoagulant medicine Pradaxa, in order to assess whether the latest available data show any higher risk than previously recognised. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the data on Pradaxa are consistent with the well-known risk of bleeding with anticoagulant medicines and that there is no change in the risk profile of the medicine, but decided that further information should be added to the product information to clarify the guidance for prescribers and patients on how to reduce and manage this risk.

What is Pradaxa?

More information tools at European level?



Pradaxa

dabigatran etexilate

About | Authorisation details | Product information | Assessment history

Next tab »

This is a summary of the European public assessment report (EPAR) for Pradaxa. It explains how the Committee for Medicinal Products for Human Use (CHMP) assessed the medicine to reach its opinion in favour of granting a marketing authorisation and its recommendations on the conditions of use for Pradaxa.

isk with

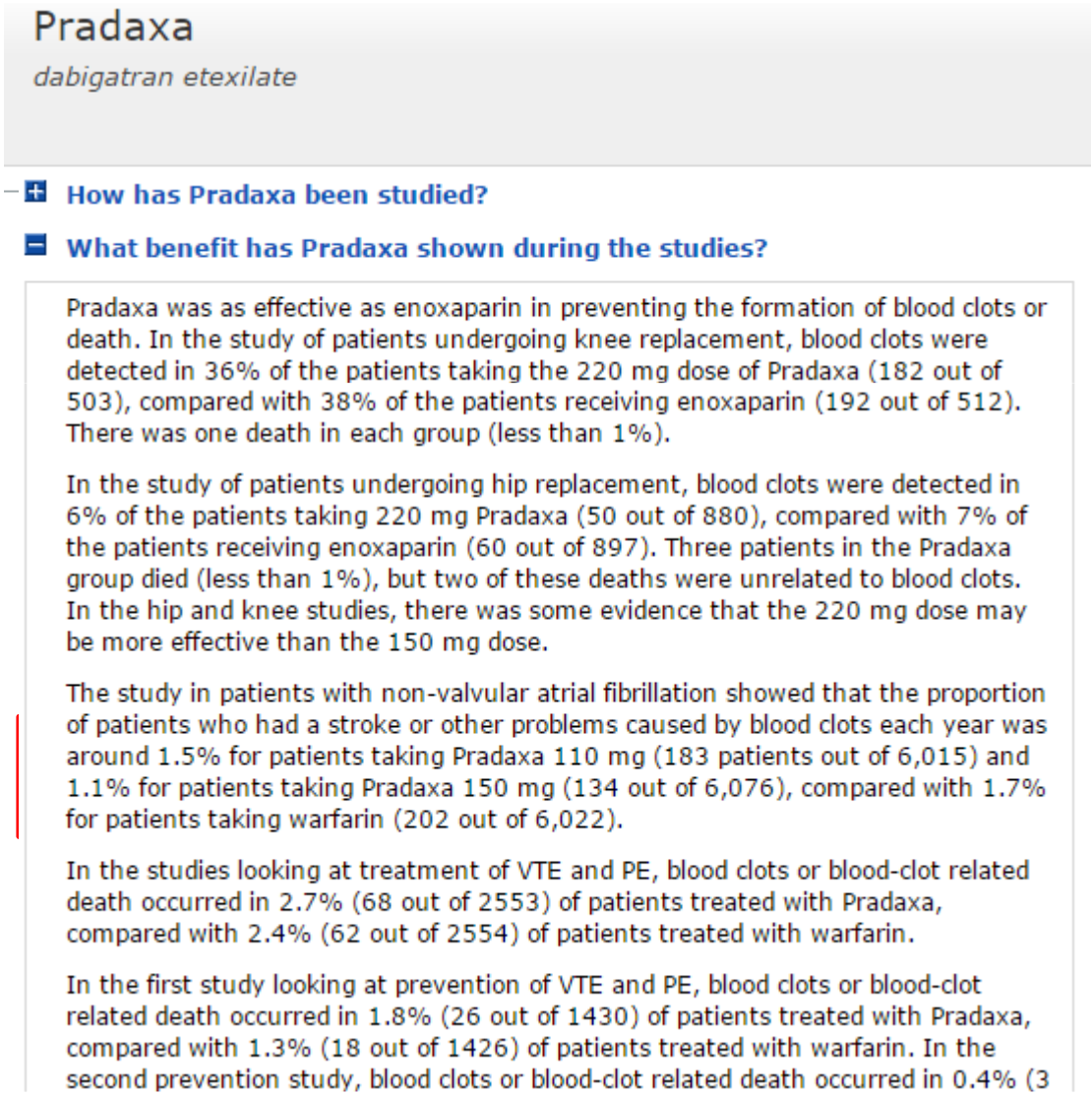
Expand all items in this list

- What is Pradaxa?
- What is Pradaxa used for?
- How is Pradaxa used?
- How does Pradaxa work?
- How has Pradaxa been studied?
- What benefit has Pradaxa shown during the studies?
- What is the risk associated with Pradaxa?
- Why has Pradaxa been approved?
- What measures are being taken to ensure the safe and effective use of Pradaxa?
- Other information about Pradaxa

ng with the
any higher
n Use
eding with
t decided
e for

More information tools at European level?

Strengthening information products from EMA (with PICOT-type tools or more graphical displays?)



Pradaxa

dabigatran etexilate

How has Pradaxa been studied?

What benefit has Pradaxa shown during the studies?

Pradaxa was as effective as enoxaparin in preventing the formation of blood clots or death. In the study of patients undergoing knee replacement, blood clots were detected in 36% of the patients taking the 220 mg dose of Pradaxa (182 out of 503), compared with 38% of the patients receiving enoxaparin (192 out of 512). There was one death in each group (less than 1%).

In the study of patients undergoing hip replacement, blood clots were detected in 6% of the patients taking 220 mg Pradaxa (50 out of 880), compared with 7% of the patients receiving enoxaparin (60 out of 897). Three patients in the Pradaxa group died (less than 1%), but two of these deaths were unrelated to blood clots. In the hip and knee studies, there was some evidence that the 220 mg dose may be more effective than the 150 mg dose.

The study in patients with non-valvular atrial fibrillation showed that the proportion of patients who had a stroke or other problems caused by blood clots each year was around 1.5% for patients taking Pradaxa 110 mg (183 patients out of 6,015) and 1.1% for patients taking Pradaxa 150 mg (134 out of 6,076), compared with 1.7% for patients taking warfarin (202 out of 6,022).

In the studies looking at treatment of VTE and PE, blood clots or blood-clot related death occurred in 2.7% (68 out of 2553) of patients treated with Pradaxa, compared with 2.4% (62 out of 2554) of patients treated with warfarin.

In the first study looking at prevention of VTE and PE, blood clots or blood-clot related death occurred in 1.8% (26 out of 1430) of patients treated with Pradaxa, compared with 1.3% (18 out of 1426) of patients treated with warfarin. In the second prevention study, blood clots or blood-clot related death occurred in 0.4% (3

More information tools at European level?

- Strengthening the role of the European Network for Health Technology Assessment (EUNetHTA)

- National agencies would be in a better position if EMA or EUNetHTA provided with some more comparative elements helping to eventually evaluate the ATV of medicines.

ISDB editors participating to this research (in alphabetical order)

Editor	ISDB bulletin	Country
Dick Bijl	Geneesmiddelenbulletin	Netherlands
Juan Erviti	Boletin de Información Terapéutica de Navarra	Spain
Maria Font	Infofarma	Italy
Giulio Formoso	Informazioni sui Farmaci	Italy
Wolf Dieter Ludwig	Der Arzneimittelbrief	Germany
Jean Louis Montastruc	Bulletin d'Information de Pharmacologie	France
David Phizackerley	Drug & Therapeutics Bulletin	UK
Blanka Pospíšilová	Farmakoterapeutické Informace	Czech Repoublic

Acknowledgement: Hans Winkler (Pharmainformation, Austria)