



HAUTE AUTORITÉ DE SANTÉ

Which proton pump inhibitors provide the greatest clinical benefit?



Julie BIGA, MD

Anne d'Andon, François Meyer, Bertrand Xerri

Department for the assessment of medicinal products, French National Authority for Health

Proton pump inhibitors (PPIs)



- **1994:** First PPI marketed in France
- **Esomeprazole**
- **Lansoprazole (including generics)**
- **Omeprazole (including generics)**
- **Pantoprazole (including generics)**
- **Rabeprazole**

- **Action:** Marked, long-lasting reduction of gastric acid production (ATP phospho-dephosphorylation reaction on cytoplasmic membrane of gastric parietal cell canaliculi)

PPIs: 4 types of indications

- ✓ Symptomatic treatment of Gastro-oesophageal reflux disease (GORD); treatment of reflux oesophagitis
- ✓ Eradication of *Helicobacter pylori*; treatment of gastroduodenal (GD) ulcers
- ✓ Treatment of GD lesions due to NSAIDs; their prevention in high-risk patients on NSAIDs
- ✓ Zollinger-Ellison syndrome



Consumption of PPI's in France

- **High: 23.5 tablets/pt/yr (2007)**
- **88% increase (2000 – 2007)**
- **46% of prescriptions inappropriate**
- **Wide price range**

Purpose

- Re-assess the actual benefit and added value of 5 PPIs (approved indications)
- Request by French Ministry of Health and National Health Insurance
- Why? Price linked to added value
- Assessment by independent committee (Transparency Committee of HAS)

Actual Benefit (AB)

1. **Severity of illness (impact in terms of morbidity & mortality)**
2. **Clinical efficacy and safety of drug**
3. **Any alternative treatment? Assessment of need**
4. **Impact in terms of public health (disease burden, impact on community health, transposability of results)**

Actual Benefit	Reimbursement rate
Substantial	65%
Moderate or low	35%
Insufficient	Not included on reimbursement list

Establishing the level of Added Value (IAB)

➤ **Criteria to quantify it?**

1. Efficacy

- « quantity of effect » : relative and absolute risk reduction, NNT, ...
- « level of evidence » : design and methodology of trials, ...

2. Effectiveness

- Extrapolation of results to the clinical practice or external validity (inclusion and exclusion criteria, compliance and modality of administration, ...)

3. Relative effectiveness over the best comparator

- direct and indirect comparisons, absence of therapeutic alternatives

➤ **What dimensions are taken into account ?**

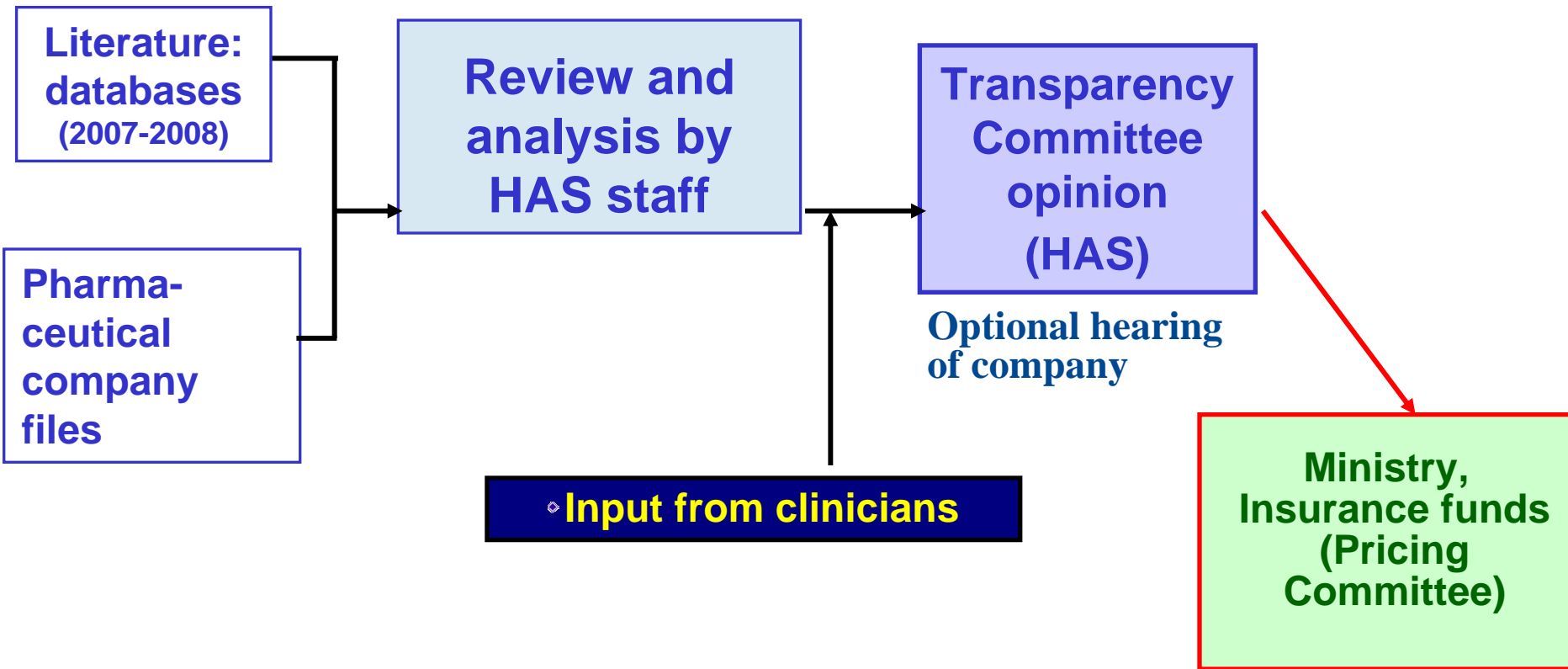
Survival rate, higher probability of full recovery, faster partial or total recovery, slower progression of diseases, quality of life, ...

Added value (Improvement in Actual Benefit (IAB))

Better than current treatments for patients?

Added value	Consequence (French Healthcare Products Economic Committee)
Major (I)	Faster access at better price (Price notification instead of negotiation)
Important (II)	
Moderate (III)	
Minor (IV)	Eligible for higher price than comparator
None (V)	Reimbursed only if cost less than that of comparator

Assessment process



Selection criteria for PPI studies

- **Patient population: only adults**
- **Meta-analyses, systematic reviews, guidelines, HTA reports, head-to-head RCTs**
- **No phase III studies vs placebo**
- **Only clinical endpoints**
- **Approved indications and doses only**

Results of internal review

New documents: 346; analyzed:64; cited in report:25; Zollinger-Ellison: 0

Efficacy

No PPI was superior to any other in any of the indications (results of direct comparisons)

- *symptomatic treatment of GORD
- *long-term treatment of reflux oesophagitis
- *eradication of *Helicobacter pylori*
- *peptic ulcer disease
- *long-term treatment of duodenal ulcers
- *treatment of gastroduodenal lesions caused by NSAIDs
- *prevention of gastroduodenal lesions in high-risk patients on NSAIDs

* erosive reflux oesophagitis

Esomeprazole (40 mg) slightly more effective than omeprazole (20 mg) on healing rate in the short-term treatment in a subgroup of patients

RR at 4 weeks =1.19 [1.02 – 1.39] NTT=17 [95% : 9 – 100]

Safety

No difference among PPIs for overall incidence of adverse events

Transparency Committee opinion

1. Efficacy of PPIs well established
 2. Update reveals good safety profile
 3. Effectiveness of PPIs well established
 4. No difference in actual benefit or added value.
- Health Ministry Decision: *awaited ...*
- Proper use leaflet for prescribers

Proper Use Leaflet



Concise (4 p), visually attractive, more practical than academic, reviewed by speciality society

Key messages

No demonstrable treatment benefit of PPIs in 3 indications:

- Functional dyspepsia
- Prevention of gastroduodenal lesions in low-risk patients on NSAIDs for acute disease
- GORD: extra-digestive manifestations

Prescribe generic drugs

What next? Leaflets for patients; impact of leaflets – 2010?

Acknowledgements

1. Patrick Semenzato
2. Pascal Potier
3. Aurélien Dancoisne
4. Caroline Tranche & Emmanuelle Cohn

Contact: j.bigga@has-sante.fr