OFF-LABEL USE IN FRANCE

- **Physician free prescribe outside scope MA**
  - *indications, dosage, prescribing and dispensing*
- **If deemed necessary to treat/stabilise patient, i.e. to answer specific needs**
- **In the absence of therapeutic alternative on the market**
- **Patient should be informed on B/R**
- **Choice to be justified**
- **Not reimbursed by social insurance**

RTU (Temporary recommandation for use)

- **LAW 29/12/12 modified 08/08/14**
- **At the initiative of ANSM, upon information of off-label use from**
  - *MAH (legal obligation)*
  - *Health ministry, HAS, ref centres rare diseases, national cancer institute,*
  - *National health insurance*
- **In the absence of marketed therapeutic alternative**
  - *Same active substance*
  - *Same dosage*
  - *Same pharmaceutical form*
- **B/R assumed favourable**

RTU (Temporary recommandation for use)

SCOPE

- Indication
- Dosage
- Prescribing and dispensing
- For 3 years (may be prolounged)

AIMS

- Secure observed off-label use
- Improve knowledge on efficacy and safety
- Encourage Companies to submit a variation
- May be reimbursed (HAS recommendation)

RTU (Temporary recommandation for use)

ANSM obligations towards MAH

- Advance notification

MAH obligations

- Provide all available information on the product in the indication
- Contribute to the proper use of medicinal products
  - *Alert ANSM on off-label-use*
  - *Set-up a follow-up on safety, efficacy and real life conditions of use → ANSM*
  - *Penalty on pricing negociations*

Physician obligations

RTU (Temporary recommandation for use)

14 RTU As per Feb 2017

- 3 in 2014 (baclofene, TNFi remicade, tocilizumab)
- 6 in 2015 (Avastin, melatonij, ustekinumab, thalidomid, bortezonib, verapamil)
- 4 in 2016 (hemangiol, MTX, Truvada, crizotinib)
- 1 in 2017 (uvesterol ADEC)
- Midazolam?

RTU (Temporary recommandation for use)

Limitations

- Low level of use by prescriber
- Administrative burden for the prescriber
- Despite alleviations in 2014 modification

2015 Request for "power excess" / 29 June 2016 decision State Council

- **Litigations on RTU from Novartis – Roche –LEEM**

→ **ALL GRIEVANCES DENIED**

- **Grievance 1: Absence of contradictory procedure**

  → *Not a MAA modification but reinforce safety of observed use*

- **Grievance 2: Contrary to EU code 2001/83/CE on MA**

  → *Not a modification of MA*

  → *planned waivers if special needs as assessed by prescriber under his responsibility (article 5(1) of directive 2001/83/CE.)*

2015 Request for "power excess" / 29 June 2016 decision State Council

- **Grievance 3: Contrary to EU regulation 726/2004 on EMA and its prerogatives**
  - → *Art 13: EU MA confers to MS same right as for a national MA*
  - → *Art 83: waiver for compassionate use/RTU falls within this waiver*

- **Grievance 4: Contrary to economic freedom due to obligations**
  - → *Existing obligations to monitor adequate use*
  - → *Restricted for public interest*
  - → *Obligations not excessive vs health issue*
  - → *Under prescriber responsibility*

2015 Request for “power excess” / 29 June 2016 decision State Council

- ***Grievance 5: Contrary to obligation of protection of public health to a high level recognized in article 168 of the Treaty on the Functioning of the European Union and in article 35 of the charter of fundamental Rights of the European Union.***

  → *Better information of prescriber due to therapeutic protocol*

  → *Safer versus observed off-label/higher level protection*

  → *B/R assumed favourable as assessed by ANSM based on data provided by MAH*

2015 Request for "power excess" / 29 June 2016 decision State Council

- **Grievance 6: EMA not consulted**
  - → *EMA role outside MA is advices and recommendations on PV, surveillance and proper use*
- **Grievance 7: Contrary to EC regulation 1394/2007 /any MA modification should be authorised**
  - → *Art 5 parag.1 Dir 2004/27/CE modified 31/03/14: waiver on demand of a health professional under his responsibility if specific needs*

Request for “power excess” on Avastin RTU/ 24 February 2017 decision State Council

Grievance 1: Exist other specialities same indication

→ *Jurisprudence 29/03/12 Eur court: waiver to authorisation for special needs as assessed by a prescriber in the absence of commercialised speciality of **same A.S, same dosage, same pharmaceutical form***

→ *Lucentis and Avastin different active substances*

Request for “power excess” on Avastin RTU/ 24 February 2017 decision State Council

- **Grievance 2: Contrary to Hospital preparation legal frame**
  - → *Processing in Hospital Pharmacy*
  - → *Strict sterile preparations of syringes*
- **Grievance 3: No direct comparison Avastin and Lucentis in specific studies**
  - →*ANSM assessed all available data*
  - →*ANSM judged B/R assumed favourable*
  - →*Jurisprudence 29/03/12 European court*
- **Refer decision June 2016 for other grievances (same as in the previous litigation)**