



The increasing use of health insurance database to evaluate drug safety : the French example

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1. The French national health insurance database (the **SNIRAM)**

2. The use of French administrative database for Pharmacovigilance (*an example*)

3. Conclusion and perspectives

Overview of French national health insurance database (SNIIRAM)

Local offices of the sickness funds

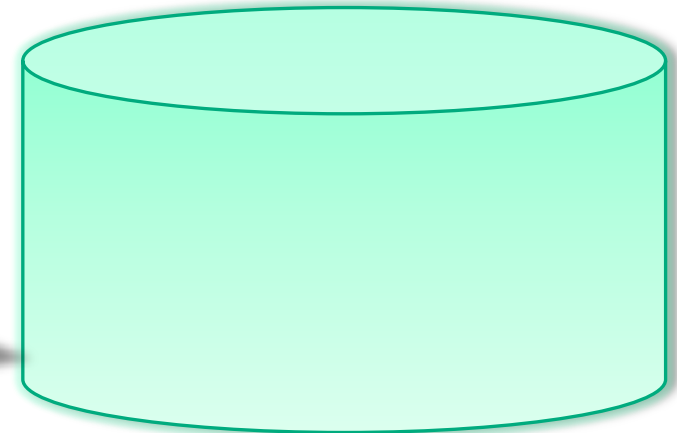
- ▶ Reimbursement of patients
- ▶ Nominative local databases

Since 2005

National Business intelligence

- ▶ Anonymous unique database

Anonymisation



Claims
Agricultural
workers

Claims
Independant
workers

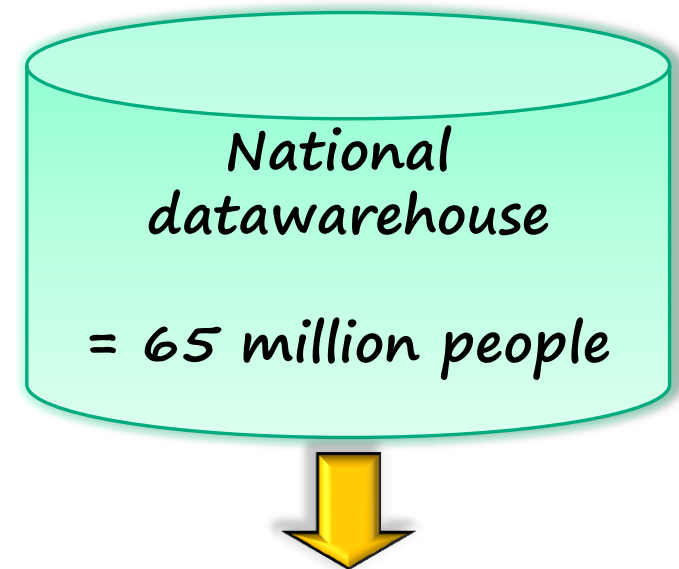
Claims
Général
schema

and.. Informations on
beneficiairies and
professionals

Overview of French national health insurance database (SNIIRAM)

National Business intelligence

► Anonymous unique database



Samples, cohorts,...

Overview of French national health insurance database (SNIIRAM)

Linkage with the national hospital discharge database (public & private) = diagnosis and main procedures performed

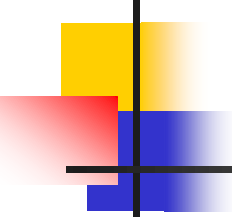
Linkage with the register of deaths (date of death)

Pilot – linkage with the register of causes of deaths

Linkage to specific external databases for research projects

National datawarehouse

Claims : Ambulatory care (procedures, drugs, lab tests coded)... but little information on diagnosis (only for patients with severe diseases)



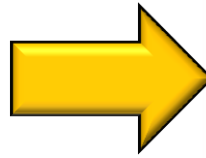
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- Weill A, Païta M, Tuppin P, Fagot JP, Neumann A, Simon D, Ricordeau P, Montastruc JL, Allemand H. **Benfluorex and valvular heart disease: a cohort study of a million people with diabetes mellitus.** *Pharmacoepidemiol Drug Saf.* 2010 Dec;19(12):1256-62.
- Neumann A, Weill A, Ricordeau P, Fagot JP, Alla F, Allemand H. **Pioglitazone and risk of bladder cancer among diabetic patients in France: a population-based cohort study.** *Diabetologia.* 2012 Jul;55(7):1953-62. Epub 2012 Mar 31.
- Fagot JP, Blotière PO, Ricordeau P, Weill A, Alla F, Allemand H. **Does insulin glargine increase the risk of cancer compared with other basal insulins? A French nationwide cohort study based on national administrative databases.** *Diabetes Care.* 2013 Feb;36(2):294-301. Epub 2012 Sep 10.
- Weill A, Dalichampt M, Raguideau F, Ricordeau P, Alla F, Allemand H, Zureik M. **Combined oral contraceptives and risk of pulmonary embolism, stroke and myocardial infarction: A cohort study of 4 million French women.** *ISOP Pisa 2/3 october 2013. Oral communication.*
- Basson M, Mezzarobba M, Weill A, Ricordeau P, Allemand H, Alla F, Carbonnel F. **Severe malabsorption associated with olmesartan : A French nationwide cohort study.** *Digestive Desase Week. Chicago. May 2014 Oral communication.*

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Request by the French
medicines agency
(January 2011)

What was the objective ?

Identification of a possible association
between exposure to **pioglitazone** and
bladder cancer occurrence

*Pioglitazone : an **oral hypoglycaemic agent**,
marketed in France since 2002*

***Pre-clinical studies in rats** : an association between
pioglitazone exposure and bladder tumours*



Methods : Design

- **Historical cohort** including **1,491,060** patients treated with antidiabetic drugs in 2006 and followed up to 2009, with comparison between exposed (**155,535** patients) and non exposed (**1,335,525**) patients to pioglitazone
- **Mean duration of follow-up** : **37.5** months
- **Outcome** : Incidence of bladder cancer (hospital discharge diagnosis (ICD-10 = C67) and specific surgical procedure)

Results : drug exposure and bladder cancer (1)

Risk of bladder cancer [*procedures and diagnoses*] in diabetic patients aged 40-79 years in the 2006 cohort, with follow-up until late 2009. Data from SNIIRAM (Cnamts)

	Overall		Men	
	HR (95%CI)	P	HR (95%CI)	P
Exp Pioglitazone (Y/N)	1.22 (1.05 - 1.43)	0.01	1.28 (1.09 - 1.51)	0.00
Exp < 10 500 mg	1.12 (0.89 - 1.40)	0.34	1.17 (0.92 - 1.48)	0.21
Exp 10 500 to 28 000 mg	1.20 (0.93 - 1.53)	0.16	1.24 (0.96 - 1.60)	0.10
Exp ≥ 28 000 mg	1.75 (1.22 - 2.50)	0.00	1.88 (1.30 - 2.71)	0.00
Exp < 360 days	1.05 (0.82 - 1.36)	0.68	1.10 (0.84 - 1.43)	0.49
Exp 360 to 719 days	1.34 (1.02 - 1.75)	0.03	1.39 (1.06 - 1.84)	0.02
Exp ≥ 720 days	1.36 (1.04 - 1.79)	0.02	1.44 (1.09 - 1.91)	0.01

Results : drug exposure and bladder cancer (2)

Risk of bladder cancer [procedures and diagnoses] in diabetic patients aged 40-79 years
Year 2006 cohort and follow-up until late 2009. Data from SNIIRAM (Cnamts)

	Overall		Men	
	HR (95%CI)	P	HR (95%CI)	P
Exp Rosiglitazone (Y/N)	1.08 (0.92 - 1.26)	0.35	1.10 (0.93 - 1.30)	0.25
Exp Metformin (Y/N)	1.03 (0.93 - 1.13)	0.60	1.03 (0.93 - 1.14)	0.58
Exp Sulfonylurea (Y/N)	0.92 (0.84 - 1.01)	0.08	0.91 (0.83 - 1.01)	0.06
Exp other antidiabetic (Y/N)	1.00 (0.90 - 1.11)	0.93	0.95 (0.85 - 1.07)	0.40
Exp Insulins (Y/N)	1.08 (0.97 - 1.21)	0.15	1.08 (0.96 - 1.21)	0.20



Results : drug exposure and other cancers

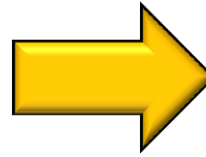
Risk of bladder cancer in diabetic patients aged 40-79 years
exposed to pioglitazone in the 2006 cohort
with follow-up until late 2009. Data from SNIIRAM (Cnamts)

Overall		
	HR (95%CI)	P
Lung cancer	0.94 (0.87 - 1.02)	0.15
Head and neck cancer	0.85 (0.73 - 0.99)	0.04
Colorectal cancer	0.97 (0.90 - 1.05)	0.45
Breast cancer (Women)	0.91 (0.89 - 1.00)	0.05
Kidney cancer	0.91 (0.79 - 1.06)	0.22



Results : Summary

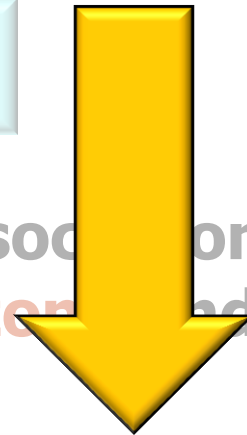
- ❖ This analysis supports the hypothesis of **a weak association** between exposure to pioglitazone and bladder cancer, with a **dose-effect relationship**
- ❖ *No increase in the risk of bladder cancer with the other oral antidiabetic drugs*
- ❖ *No increase in the risk of other cancers associated to pioglitazone*



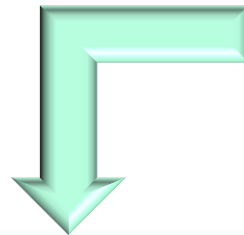
Request by the
French medicines
agency (**January
2011**)

What was the objective ?

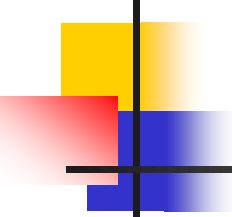
Identification of a possible association
between exposure to **pioglitazone** and
bladder cancer occurrence



... which decided to **suspend
the use of pioglitazone** in
France in **June 2011**



European Medicines Agency (**21 juillet**) recommends new
contra-indications and warnings for pioglitazone to reduce
small increased risk of bladder cancer. Benefit-risk balance
remains positive in a limited population of type 2 diabetics.




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Conclusion and perspectives



Interest of health administrative databases for safety monitoring ?

- ✓ **Large** sample size (the whole French population),
- ✓ **Comprehensive** and **detailed** information,
- ✓ **No loss of follow-up**...
- ✓ **Rapid** Response (6 months...),
- ✓ Studies carried out by the health authorities
(**independence**)





Conclusion and perspectives

- ✓ Safety studies performed on **varied databases**
(Internationale cooperation) ?
- ✓ Development of **biostatistical methods**... for
detection of safety signals...
- ✓ Or for others studies such as **comparative effectiveness**.