**Translation**

# "New LEVOTHYROX FORMULA: a "totally unexpected frequency" of reporting of adverse reactions

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*https://www.vidal.fr/actualites/22566/nouvelle_formule_de_levothyrox_nombre_totalement_inattendu_de_signalements_d_effets_indesirables/*

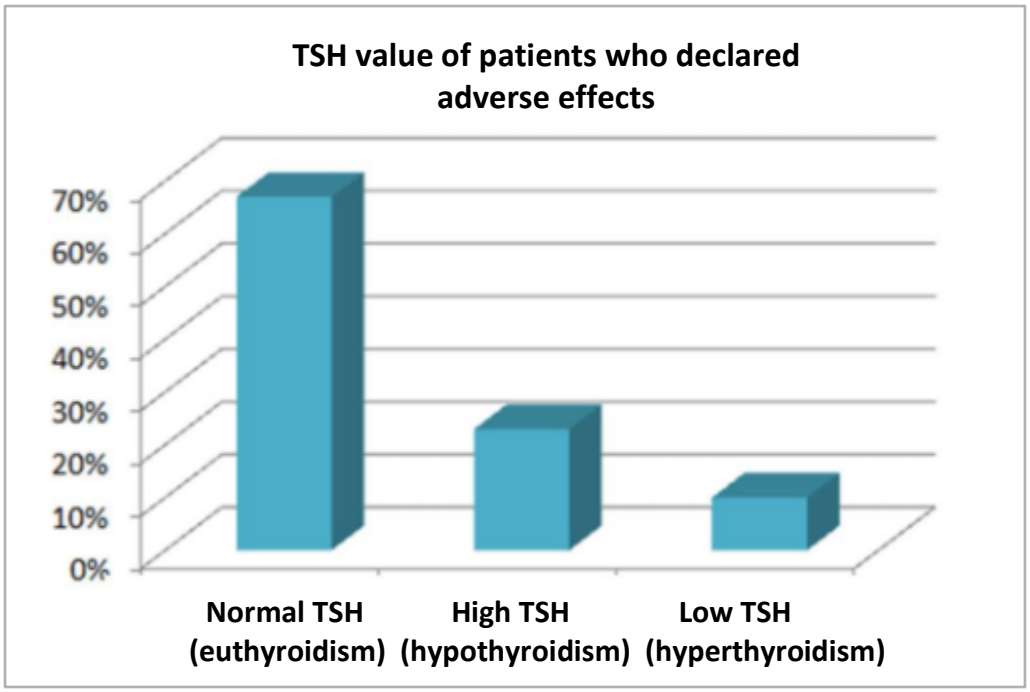
**The national pharmacovigilance survey of the ANSM** (the French National Agency for Medicines and Health Products Safety) published on 30 January 2018 shows a **"totally unexpected frequency of reporting"** of adverse reactions with the new formula of LEVOTHYROX. Moreover, in **2/3 of the cases, they occur without biological thyroid imbalance** (when adequate follow-up of TSH has been carried out).

It should also be noted that the **peak of declarations of symptoms was in June/July 2017** – before the media crisis following testimonies of associations or leading figures in the media, which **relativizes the argument advanced by the ANSM of an "amplifying effect due to the new reporting portal and social networks"** (and which also relativizes, even invalidates, the hypothesis of a *nocebo* effect).

Moreover, according to the authors of this report, **these adverse reactions are not new, specific to this new formula**. But **no explanation is advanced** to explain these adverse effects, mixing signs of hypo and hyperthyroidism with normal or disturbed blood test values.

In order to further explore the consequences of this change in formula and the subsequent arrival of other levothyroxine-based drugs, the ANSM will conduct further investigations, particularly from health insurance data (SNIIRAM data base).

For **Claude Pigement**, vice-president of the ANSM interviewed on 30 January by *Le Parisien*, **the gap widens between medical elites and patients**. These investigations should thus also be completed by the "**publication of the entire pharmacovigilance report of 2012**" from which originates the change of formula (a report only available in a summarized format, which preoccupies the patient associations).




The TSH value was within the normal range for 67% of the patients taking the new LEVOTHYROX formula and submitting a declaration of adverse effects

## A pharmacovigilance report completing the report published in October 2017

The launch of the **new LEVOTHYROX formula in March 2017** was accompanied by the start of a **national pharmacovigilance survey by the ANSM**.

The first results of this survey (the "first survey") were published in October 2017. They in particular showed **a high frequency of reports** and the **occurrence of signs of hypo or hyperthyroidism in spite of TSH assays within the expected standards**, which intrigued the authors of the report (see article (in French) on VIDAL.fr).

**The ANSM then published on 30 January 2018 the additional data** from the analysis of the declarations submitted between 15 September and 30 November 2017 (the "second survey").

## More than 17,000 reports of adverse effects to the authorities

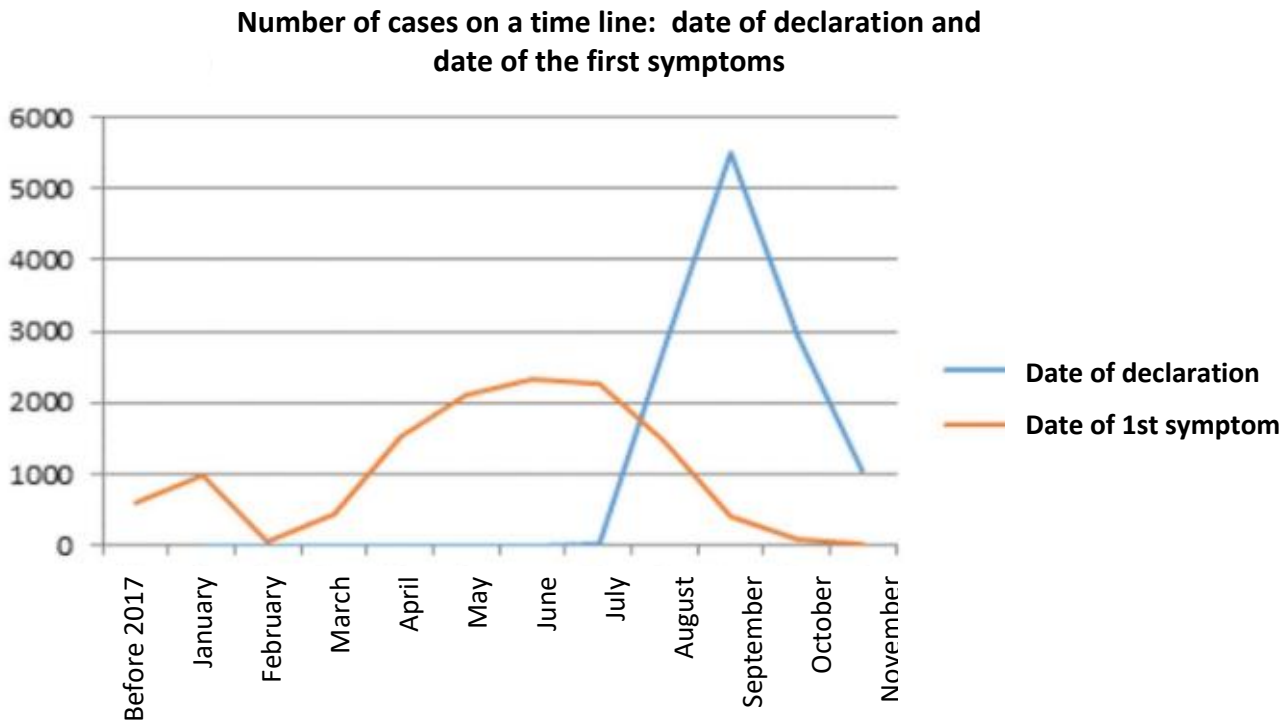
Reports of adverse effects from patients taking LEVOTHYROX registered in the national pharmacovigilance basis (via the *signalement-sante.gouv.fr* web portal) have amounted to **17,310 since March 2017** (0.75% of the 2.3 million users of the new formula): **5,062 during the first survey** (end of March – mid-September 2017) and **12,248 during the second survey** (mid-September – end of November 2017).

This high frequency was qualified by the authors of the report as **"unprecedented" and "totally unexpected ".** It is also necessary to add some or all of the **18,000 reports made directly to Merck** since March 2017 (it is difficult to know whether these reports are duplicates, or not, of those made on *signalement-sante.gouv.fr*).

## A peak of symptoms that occurred before media coverage

The majority of these adverse reactions occurred **between April and September 2017**, with a **maximum in June and July**, which seems to reduce the role of media coverage, and therefore also excludes, at least partially, the potential role of a *nocebo effect* (perception of unusual symptoms as a result of rumors, media coverage of such symptoms, or simply by reading the package insert).

Nevertheless, the **entering date of these adverse events mainly occurred in September**, after the outbreak of the crisis, as summarized in this graph of the ANSM:



## On average, patients reported 5 adverse reactions

Patients reported an average of **5 adverse effects** (from 1 to 36). The majority were **women** (90.4%, knowing that this drug is also used mainly by women), the **average age was 55 years** (± 13 years). The number of **pediatric cases** was 17.

## General, neuro-psychiatric, musculoskeletal symptoms: list of the most frequently reported adverse reactions

The adverse reactions reported to the authorities are **similar in the first survey and the second survey**, with an overall predominance (by order of frequency) of:

- **General symptoms**: fatigue (9.4% of all reports), asthenia (3%).
- **Nervous system disorders**: headaches (6.2%), migraine (1.1%), disturbance of attention (1.2%), amnesia (1.1%).
- **Psychiatric disorders**: insomnia (4.5%), sleep disturbance (1.2%), irritability (1.8%), depression (1.5%).
- **Musculoskeletal disorders**: Muscular contractures (4.2%), muscle aches (2.8%), joint pain (2.3%).
- **Gastrointestinal disorders**: nausea (2.4%), diarrhea (1.6%).
- **Alteration of clinical or biological measures**: weight gain (3%), increased TSH (1.7%).
- **Skin conditions**: Hair loss (4.7%), sweats (1.2%)
- **Ear ailments**: dizziness (5.5%), tinnitus (0.2%).
- **Cardiac disorders**: palpitations (1.8%), tachycardia (0.9%), arrhythmia (0.2%).
- **Visual disorders** (0.9%).
- **Respiratory ailments**: dyspnea (0.8%).

The **symptoms reported directly to Merck between March and late November are of the same order**, with a predominance of general, neuro-psychiatric and musculoskeletal symptoms.

## 19 cases of deaths were reported and analyzed, with no proven link to the new LEVOTHYROX formula

According to the ANSM, for the 19 deaths recorded in the pharmacovigilance database (dizziness and death at 85 years old, fetal death, acute respiratory failure, suicide, etc.), "*it is not possible to assess or to formally exclude a link with the taking of the new LEVOTHYROX formula*".

## In 2/3 of the reports adequately documented, TSH level was normal

**1,745 reports of adverse reactions** included sufficiently documented biological analysis.

The analysis of these 1,745 reports shows that if symptoms are reported:

- **67%** (1,172 declarations) were associated with **normal TSH** (euthyroidism).
- **23%** (394 declarations) were associated with **high TSH** (hypothyroidism).
- **10%** (179 cases) were associated with **low TSH** (hyperthyroidism).

These proportions remain unchanged when the analysis is carried out by **age groups**, or according to **BMI** (*body mass index*).

**Symptoms are close, whether patients have low, normal, or high TSH**, although quite logically, the number of neuro-psychiatric and cardiac disorders appears to be somewhat higher in case of hyperthyroidism.

Likewise, **the distribution of biological results appears similar depending on the indication** for which LEVOTHYROX is used.

## Biological discordance – symptoms already seen before

The ANSM noted that a recent study has already revealed the **occurrence of abnormal symptoms under levothyroxine with normal TSH** (*Mc Millan et al. 2016*).

Another study (*Hennessey et al. 2010*) showed the **onset of symptoms of both hypo and hyperthyroidism in patients whose TSH varied**, following a change in formula (89%) or not (11%).

Other studies have attempted to analyze the link between changes in TSH and depressive symptoms, but with results that are difficult to interpret – different populations, ages, numbers, etc.

**Recognition of the possible negative impact of some of these adverse effects**

The report on the pharmacovigilance survey stresses "**the weight of the 339 adverse effects considered as severe in terms of discomfort in daily life**, reported by patients (driving and walking in particular)."

**The adverse effects in general occurred quickly, and in many cases disappeared when switching to another brand (which is possible since fall 2017)**

In one out of two cases, the adverse reactions appeared on average **within a period of less than 1 month after the transition to the new LEVOTHYROX formula**.

The **symptoms improved in 20% of cases,** "**especially among those who switched to another brand**", which "reinforces the importance of [progressively] providing therapeutic alternatives" since autumn 2017.

However, patients who have switched to another brand may have struggled to continue their treatment with the same alternative, due to **supply difficulties**.

**"No satisfactory hypothesis to explain the occurrence of these effects"**

**At the end of their analysis, the authors of the report are perplexed**, unable to identify potential patients at risk or to formulate a satisfactory hypothesis to explain the occurrence of these non-specific adverse reactions, with or without TSH disturbance, evoking signs of hypo or hyperthyroidism.

Similarly, the authors **cannot identify a direct link between the onset of these symptoms and the composition** of this new LEVOTHYROX formula.

**Nationwide study**

This survey of pharmacovigilance reports will be **completed by the studies carried out by the *Epidemiology of health products* department** of the ANSM based on the health insurance database (SNIIRAM), including a study of use and a study of risk.

**For the vice-president of the ANSM, the gap is widening between the medical elite and the patients. So we have to go further to explain this phenomenon.**

As we have seen, a **significant number of adverse reactions have been reported**, which can not be directly attributed to a possible nocebo effect of the media crisis of September 2017 (symptoms felt most often before this crisis). Moreover, these **adverse effects may involve signs of hypo and hyperthyroidism**, whereas they **mostly occur at normal TSH**.

As the above summary of the report recognizes, **there is no explanation for this phenomenon**, although **it has probably been aggravated by unfavorable circumstances** (monopoly of LEVOTHYROX in France, no pilot experimentation, minimum communication of the ANSM and absent communication from Merck, minimization of symptoms by public bodies, even some doctors, disrespect of associations, media crisis, petitions and court proceedings, etc.).

**Claude Pigement (vice president of the ANSM**, with no executive role), interviewed by *Le Parisien* on January 30, 2018, is also concerned with **"the widening gap between the assertions of a medical elite and the word of patients**", who live daily with their symptoms, and this while the *Kouchner Law* of 2002 and the *Touraine Law* of 2016 have yet reaffirmed the important place of patients.

He considers that "**since there is a total lack of understanding between the public authorities and associations, a precise scientific study of what happened with this medicine becomes necessary,** especially since 67% of patients had normal TSH."

**Need to publish the pharmacovigilance report of 2012 in its entirety; to rethink the communication of the ANSM … and of the "eminent professors"**

Mr. Pigement estimates that the **publication of the entire pharmacovigilance report of 2012 is necessary** (note: this report, which originated the request to change the formula, is resumed on page 15 and 16 of the report – but has still not been published, despite the requests from the patient associations).

Claude Pigement also outlines a **lack of responsiveness of the ANSM**, which "**underestimated the sensitivity of this drug and did not deliver the appropriate information**", **leaving the sick "devoid and angry**." He finally **denounces the "eminent professors"** who have entrenched behind the" nocebo effect, a simplistic solution".

**Additional information** (mostly in French):

**Point d'actualité sur le Levothyrox et les autres médicaments à base de lévothyroxine : Les nouveaux résultats de l'enquête nationale de pharmacovigilance confirment les premiers résultats publiés le 10 octobre 2017**, ANSM, 30 janvier 2018 (rapport complet, 57 pages)

McMillan M et al. **Comorbidities, Concomitant Medications, and Diet as Factors Affecting Levothyroxine Therapy: Results of the CONTROL Surveillance Project**. Drugs R D. 2016; 16(1):53-68.

Hennessey JV et al. **Adverse event reporting in patients treated with levothyroxine: results of the pharmacovigilance task force survey of the american thyroid association, american association of clinical endocrinologists, and the endocrine society**. Endocr Pract. 2010;16(3):357-70.

**Levothyrox : «Il faut une étude scientifique précise de ce qui s'est passé»**, Le Parisien, 30 janvier 2018

**Commission Nationale De Pharmacovigilance, compte rendu de la réunion du mardi 27 mars 2012**

**On VIDAL.fr**

**EUTHYROX : le Conseil d'Etat rejette une plainte, Merck annonce la fin prochaine de son importation** (décembre 2017)

**LEVOTHYROX : premiers résultats de l'enquête de pharmacovigilance de l'ANSM, des zones d'ombre persistent** (21 octobre 2017)

**L-THYROXIN HENNING (lévothyroxine) : 4 dosages disponibles à partir du 16 octobre** (12 octobre 2017)

**Levothyroxine : aides à l'initiation et à la gestion des difficultés, nouvelles importations d'EUTHYROX** (5 octobre 2017)

**LEVOTHYROX : précisions et actions suite aux inquiétudes et plaintes de certains utilisateurs** (août 2017)

**LEVOTHYROX (lévothyroxine sodique) comprimé sécable : nouvelle formule, nouvelles couleurs** (mars 2017)

**Cancer de la thyroïde : face au surdiagnostic massif et ses conséquences, le CIRC appelle à la prudence** (août 2016)
Sources : Le Parisien, ANSM (Agence Nationale de Sécurité du Médicament)