The Autorité de la concurrence imposes a fine of 25 million euros on Janssen-Cilag laboratory and its parent company Johnson & Johnson for having first prevented then restricted the development of generic versions of Durogesic, its originator medicinal product.

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Background

Following a referral by the pharmaceutical laboratory Ratiopharm[1], now Teva Santé, the *Autorité de la concurrence* has today issued a decision imposing a fine of 25 million euros on Janssen-Cilag and its parent company Johnson & Johnson for having delayed the arrival to the market of a generic version of the Durogesic and for then blocking the development of this generic medicinal product.

Durogesic is a powerful opioid analgesic, with the active ingredient fentanyl, prescribed for treatment of severe pain. It is provided to patients with chronic cancer pain, including children.. It is prescribed in the form of a patch to be applied to the skin.

Two practices led to the imposition of the fine:

- repeated legally, and unjustified, approaches of Janssen-Cilag, to the AFSSAPS (the French agency for medical safety of health products[2]), with the aim of convincing the health authority to refuse to grant, at a national level, generic status to competing medicinal products from the Durogesic , despite this status being

obtained at European level.

- implementation by Janssen-Cilag of a major campaign falsely disparaging the generic versions of Durogesic among office- and hospital-based healthcare professionals (doctors, pharmacists) using misleading language to create doubt in their minds concerning the effectiveness and safety of these generic medicinal products.

These are grave practices. They have delayed the arrival to the market of generic medicines by several months and have discredited the generic versions of Durogesic, irrespective of any consideration of public health, by creating doubt in the minds of healthcare professionals regarding their effectiveness and safety.

The strategy implemented by Janssen-Cilag had large-scale effects targeting all the healthcare professionals likely to prescribe or dispense Durogesic and generated a loss of income for the generic medicinal product laboratories in a context marked by chronic deficits in their corporate accounts.

1.LEGALLY UNJUSTIFIED APPROACH BY JANSSEN-CILAG TO THE FRENCH HEALTH AUTHORITY

Following the issue of a marketing authorisation (AMM) by Germany for its generic medicinal product, Ratiopharm instigated a mutual recognition procedure, as allowed under European legislation, with the aim of obtaining a marketing authorisation in the member countries of the European Union - including France - where it wished to distribute its medicinal product. The European Commission granted this marketing authorisation in October 2007 and ordered the member countries to comply with it within 30 days. However, Janssen Cilag interfered unduly in the national procedure for issuing the

marketing authorisation with an objective to delay the arrival to the market of generic medicines.

- *Repeated unjustified approaches by Janssen Cilag to the AFSSAPS*

During the procedure to issue marketing authorisation to generic versions of the Durogesic, Janssen-Cilag wrote, on multiple occasions, to the AFSSAPS, and requested the organisation of a meeting with it. During these exchanges, the laboratory called the decision of the European Commission into question and suggesting that the AFSSAPS was able to make a different decision from the one made at the European level, whereas the Commission's decision was in fact legally imposed on the French agency.

In order to convince the AFSSAPS, the laboratory questioned the quality of the generic medicinal products in competition with Durogesic, in particular questioning the bioequivalence, despite it having been established, and the existence of differences in the qualitative and quantitative composition of the active ingredient, fentanyl.

> It proposed in a letter that Durogesic and its generic counterparts were not "exactly similar".
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> In an account sent to the AFSSAPS, Janssen-Cilag even went as far as questioning the whole class of generic medicinal products by indicating that "*the system in place does not offer all the necessary safety provisions*" and that reasons of cost led the laboratories to "*look for sources of supply outside the European Union, involving countries that do not always offer the required guarantees of quality (e.g. Asia)"*

It also put forward risks for public health that this substitution could cause in some patients: ineffectiveness or adverse effects triggering an increase in pain.

> Janssen Cilag proposed that the substitution could generate "ineffectiveness or unexpected adverse effects among some types of patients (elderly or frail)", (...) "*Any substitution used for children could cause similar or even worse problems"*

- *An extremely long marketing authorisation for the generic medicinal products*

The AFSSAPS, being aware of the alarmist arguments presented by Janssen-Cilag, and having responsibility for guaranteeing health safety, initially refused to recognise the generic status of the medicinal products in competition with Durogesic even though it had no margin for manoeuvre to ask as such, in view of the Decision by the European Commission.

> In a letter sent by the AFSSAPS to Ratiopharm, the health agency justified the refusal to grant the generic status to the medicinal product, by stating that "*the quantity of active principle contained in a patch [the Ratiopharm medicinal products] is not the same as that contained in a patch of the reference product Durogesic (…)".*

The objective that Janssen-Cilag had set in 2005 at an internal meeting of a group called "Team ANTI-Génériques Durogesic®", was achieved. It was only at the end of 2008, more than a year after the Commission decision, that the AFSSAPS granted generic status to the competing medicinal products from the Durogesic, with a warning attached to this authorisation, recommending careful medical monitoring of certain patients (those with fever, elderly patients and children) in the event of changing between fentanyl-based medicinal products.

2. AN ORGANISED GLOBAL ADVERTISING CAMPAIGN ATTEMPTING TO DISCREDIT COMPETING MEDICINAL PRODUCTS FROM THE DUROGESIC

- *Mass communication with healthcare professionals*

After the marketing authorisation for the transdermal fentanyl, Janssen-Cilag used various means to deliver a message extensively to hospital and office-based doctors and pharmacists, denigrating the competing medicinal products from the Durogesic, presenting them as generics that are not like the others.

This message emphasised the differences in the quantity of the active ingredient contained, between the various patches, as well as their size difference.

> The originator laboratory recommended that its medical sales representatives should emphasise that the generic patches "*do not have the same composition, nor the same quantity of fentanyl nor the same size as the Durogesic® patch".*

Janssen-Cilag thus suggested that the procedure for granting the marketing authorisation to generic medicinal products would not be sufficiently protective of the health and safety of patients, by insisting in particular on the ligntened nature of the files provided as they were containing only the bioequivalence studies.

To convey this message, 300 medical sales representatives, designated as "commandos" were trained. A medical newsletter was distributed extensively to all doctors, and office- and hospital-based pharmacists by post, e-mail, fax and in the specialist press. Distance training and telephone calls from doctors to dispensing pharmacists were added to the strategy.

> The implementation of the above actions has been confirmed by many testimonies:
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> *During the investigation, the following statement was taken from one pharmacy, located in Paris: "when the generic came out, the laboratory called us to advise us to continue with Durogesic® for treatments that had already been started using this product (and not to change over to the generic) (…) The laboratory producing Durogesic® also offered us training at the time of release of the generics like Durogesic®. This training covered the product, how it was to be dispensed, etc."*
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> The pharmacy in a shopping centre in Lyon stated: "We received the visit from Janssen-Cilag at the time of release of the generic. The person who

came (…) advised us not to dispense the generic. "

The head pharmacist at the Roanne medical centre stated that the medical sales representatives from Janssen-Cilag informed him during one visit of "the arrival of competitor products (Nycomed, Ratiopharm) that were "not generic" and therefore "unable to be used as a substitute".

• *Misuse of the AFSSAPS warning*

The laboratory distorted the content of the warning issued by the AFSSAPS by providing an inaccurate and incomplete presentation of the risks associated with substitution, thus conveying an alarmist message to the healthcare professionals. The AFSSAPS also sent a letter to Janssen-Cilag, in order to correct the inaccuracies in the letter sent to the pharmacists because certain phrases "*did not accurately reflect the content of the position held by the AFSSAPS*".

In the "*medical newsletter*", Janssen Cilag emphasised the risk associated with replacement of the originator medicinal product with the generic version, whereas the warning provided by the AFSSAPS made no distinction between substitution either way ("*reference medicinal product replaced by generic version, generic medicinal product replaced by reference medicinal product or generic medicinal product replaced by generic medicinal product*").

In addition, the warning listed specific risks of changing treatment for certain categories of patients (patients with fever, elderly patients and children), whilst stating that these risks could be eliminated by medical monitoring. Yet the laboratory did not specify the categories of patients nor did it state that monitoring could be implemented. On the contrary, it suggested that any change of fentanyl patch during treatment could entail a particular risk, and was therefore to be avoided.

"*Please do not change from one patch to another during treatment", as "a patient who has started treatment with Durogesic® should preferably continue to use Durogesic®" or even "ensure that there is no change in the brand of fentanyl patch during treatment"*

Screensavers installed on doctors' computers also mentioned a "special" warning, showing the text of the warning surrounded by some triangular signs indicating the presence of a danger.

Lastly, Janssen-Cilag emphasised the allegedly exceptional nature of the warning applied by the AFSSAPS, whereas this option had only been introduced into the public health code a short time beforehand.
These statements generated an extensive response among healthcare professionals. The result was that doctors and pharmacists were reluctant to dispense the generic medicinal products, for fear that it would engage their liability:

> A cancer specialist in practice in Lille pointed out: "*The sales representative warned me of the risk for patients (…) the message from these representatives was very forceful. They applied pressure to get their message over. This message was attempting to make me feel guilty, for example suggesting that the patients that I might prescribe the generic for would be overwhelmed by pain" (refs 38720 and 38721*).

> A pharmacy, in Lyon, stated: "*We had received a message about the lower effectiveness of the generic [of Durogesic®] and were not inclined to change. All the more so because the prescriptions showed the note "non substitutable''*

This misleading presentation sparked serious concerns among healthcare professionals, generating an even more extensive, response as there is still a certain reluctance from them towards generic medicinal products, which can be possibly explained by the lack of awareness regarding the marketing authorisation procedure, by a poor assessment of the regulatory framework on substitution and by their desire to guard against the risks that could engage their civil or legal liability.

Grave practices, on a large scale, which have taken a toll on corporate accounts

The practices applied by Janssen-Cilag are grave. They delayed the arrival to the market of generic medicinal products and restricted their growth.

With its repeated interventions to the AFSSAPS, Janssen-Cilag managed to delay the marketing authorisation procedure for the competing medicinal products from the Durogesic by several months, as well as the recognition of their status of generic medicinal products. The originator laboratory could thus unduly benefit from its longer monopoly situation in the concerned markets.

During this period, the foreclosure effect on competitors from the Durogesic was almost absolute, by making the marketing of competing generic medicinal products from the Durogesic impossible, generating a loss of income for the generic medicinal product laboratories in a context marked by chronic deficits in their corporate accounts.

The smear campaign implemented by the office- and hospital-based healthcare professionals was vast, as shown by the target audiences affected:

- 12,800 pharmacies were affected by the peer-to-peer discussions, in other words just over half of French pharmacies.

- 83 % of pharmacists asked by Janssen-Cilag, as part of a study evaluating the effects of its campaign, had memorised "*the risks associated with changing between fentanyl-based medicinal products*";

- 12,000 GPs have the screensaver, in particular.

This smear campaign, implemented between 2008 and 2009, contributed to the low penetration rate of the generic medicinal products from the Durogesic, by amplifying the effects of the warning adopted by the AFSSAPS, participating in the decision of the public authorities to impose, in January 2011, a a flat-rate liability price[3] after observing that the substitution targets had not been achieved. Janssen-Cilag itself had not anticipated such a low substitution rate as that seen.
Consequently, the Autorité has imposed a fine of 25 million euros against Janssen Cilag and its parent company Johnson & Johnson.

[1] Ratiopharm had also requested the ordering of interim measures. The Autorité refused this request, considering that the necessary conditions had not been met, but had decided to pursue an investigation into the merits of the case. In 2015, Teva withdrew their request.

[2] The AFSSAPS has since become ANSM (national agency for safety of medicines and health products).

[3] The flat-rate liability price is used to impose a single nominal sum for reimbursement for originator and generic medicinal products alike, freeing the dispensing pharmacist from his obligation to replace the originator medicinal product with the generic version

As a reminder, the Autorité has previously already applied penalties for defamatory practices against pharmaceutical laboratories

In 2013, the *Autorité de la Concurrence* fined the Sanofi-Aventis laboratory 40.6 million euros for having implemented a strategy discrediting the generic versions of Plavix® (see press release of 14 May 2013).

In the same year, the *Autorité de la Concurrence* fined the Schering-Plough pharmaceutical laboratory 15.3 million euros for having hindered the arrival of the generic version of its originator medicinal product Subutex® (see press release of 19 December 2013).

DECISION 17-D-25 OF 20 DECEMBER 2017

See the full text of the decision