Implications of the French early access reform for the pharmaceutical industry

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Introduction & Objectives

In July 2021, the reform to the temporary authorisation for use (Autorisation Temporaire d'Utilisation, ATU) system became effective, after being initially published within the 2021 healthcare plan on 14th December 2020 (Article 78- Loi de financement de la sécurité sociale, FSSL). Among key changes, the reform introduced the need to meet three criteria for eligibility: ability to presume innovation vs. the most clinically relevant comparator(s), evidential support from an appropriate development plan and an absence of significant safety or tolerability unknowns[1]. The company is still able to set a free price, but the mechanism for paying back the difference with the final negotiated price is now based on based on actual revenues, rather than pre-paid based on forecasted revenues. This article aims to look at the learnings, a year into the reform, and reflect on whether the implications for the pharmaceutical described in our article published in EPR in June 2021[2] have materialised.

Methods

This study scrutinizes the application of all 30 non-COVID related product applications submitted for an Autorisation d'accès précoce (AAP, which includes the previous cohort ATU) between July 2021 and July 2022. The three evaluation criteria of the presumption of innovation developed by the Haute Autorité de Santé (HAS) (i.e., new treatment approach with an appropriate development plan and that addresses an unmet medical need) were analyzed. Additionally, the ASMR and SMR ratings were recorded for products assessed and correlations with AAP authorization were explored.

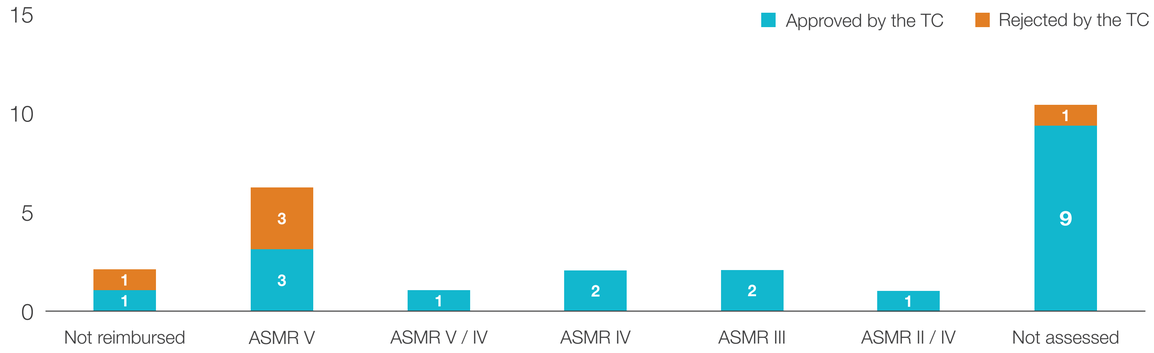
Product	Date of decision	Disease indication
Trodelvy	01/09/2021	Unresectable or metastatic triple-negative breast cancer
Onureg	15/09/2021	Acute Myeloid Leukaemia
Opdivo & Yervoy	15/09/2021	Unresectable malignant pleural mesothelioma
Opdivo & Yervoy	22/09/2021	Metastatic colorectal cancer
Adtralza	27/10/2021	Moderate to severe atopic dermatitis
Abecma	03/11/2021	Relapsed and refractroy multiple myeloma
Keytruda	03/11/2021	Unresectable or metastatic locally recurrent triple-negative breast cancer
Rinvoq	17/11/2021	Moderate to severe atopic dermatitis
Opdivo	19/01/2022	Gastro oesogastric junction or oeasophageal cancer
Tebentafusp lm.	19/01/2022	Unresectable or metastatic uveal melanoma
Minjuvi	27/01/2022	Diffuse large B-cell lymphona
Aspaveli	09/02/2022	Paroxysmal nocturnal haemoglobinuria
Opdivo	09/02/2022	Advanced or metastatic gastro oesogastric junction or oeasophageal adenocarcinoma
Qinlock	16/02/2022	Advanced gastrointestinal stromal tumour
Tavneos	16/02/2022	Polyangiitis granulomatosis or microscropic polyangitis

Product	Date of decision	Disease indication
Gavreto	09/03/2022	Non-small cell lung cancer
Keytruda	09/03/2022	Triple-negative breast cancer
Keytruda	09/03/2022	Advanced or recurrent endometrial cancer
Lenvima	09/03/2022	Advanced or recurrent endometrial cancer
Xenpozyme	09/03/2022	Acid sphingomyelinase deficiency
Kaftrio & Kalydeco	23/03/2022	Cystic fibrosis
Keytruda	23/03/2022	Unresectable or metast. HER-2 neg. esophageal cancer or gastroesophageal junction adenocarcinoma
Kimozo*	23/03/2022	High-risk neuroblastoma
Scemblix	06/04/2022	Chronic myeloid leukaemia
Lumykras	20/04/2022	Non-small cell lung cancer
Rybrevant*	20/04/2022	Non-msall cell lung cancer
Voraxaze	20/04/2022	Reduce the toxix plasma concentration of methotrexate
Kapruvia	20/04/2022	Severe pruritus (associated with chronic renal failure in the context of haemodialysis
Retsevmo	11/05/2022	Advanced medullary thyroid cancer
Padcev	01/06/2022	Adanced or metastatic urothelial carcinoma

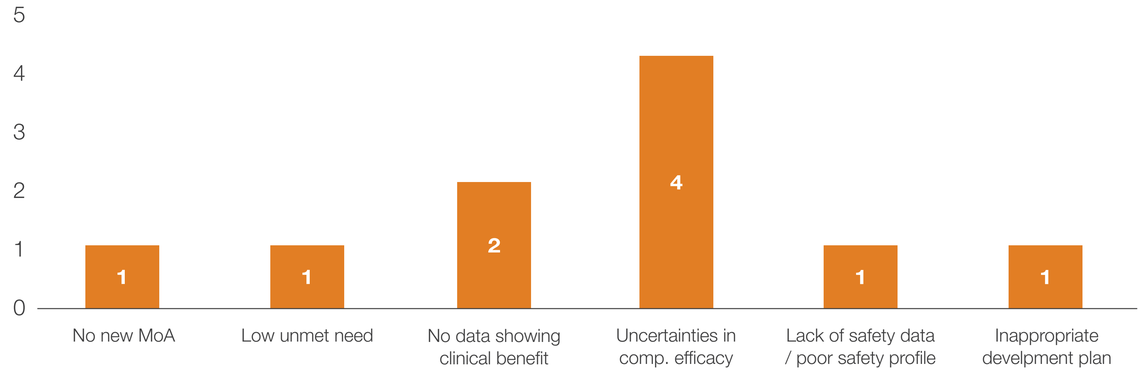
AAP approved AAP rejected

*Products rejected by the TC but approved by HAS

Results



ASMR ratings acheieved for products approved or rejected by the TC



Number of mentions of each of the factors that led to rejection by the TC

Among the 30 applications, 22 (i.e., 73%) concerned oncology products; the rest was submitted for the treatment of cystic fibrosis, atopic dermatitis and other diseases. 90% (n=27) were successful and received an AAP; this is in line with the statement from the HAS in May 2022 that showed 90% of applications submitted since the reform led to early access authorisation[3]. All successful applicants were considered to address a high unmet need disease and 81% (n=22) demonstrated a known and acceptable safety profile. 20 out of the 27 approved applications presented comparative data showing superior benefits (vs. placebo or SoC). Other drivers included demonstration of acceptable development plan.

The need for comparative evidence to drive a positive assessment varied across decisions. In the case of Abecma in multiple myeloma adult patients refractory to at least three treatment options, the data submitted was a single-arm Phase 2 trial. This was deemed acceptable given the concurrence of comparative studies vs. SoC and was further supported by input of external experts on the expected benefit in patients with no other remaining treatment options[4]. In other cases, such as Opdivo and Yervoy in the treatment of adult patients with metastatic colorectal cancer[5], the lack of comparative results was the main factor leading to product rejection.

Three specific evaluations are worth noting. Firstly, Gavreto, a monotherapy against advanced non-small cell lung cancer, was rejected despite meeting every criteria of presumption of innovation. The TC however considered the unmet need to be low because of already available appropriate treatments and criticized the uncertainties around the comparative effectiveness and positioning of the product[6]. In two other exceptional cases, the HAS granted AAP to Kimozo and Rybrevant against the TC advice because they considered their availability could not be postponed given the absence of existing treatments and despite the absence of safety data for Kimozo and comparative data for Rybrevant[7,8].

All products with a rejection from the TC (including Kimozo and Rybrevant) achieved ASMR V or AMSR IV / V in the case of Rinvoq or no reimbursement when assessed for reimbursement, while only 5 products with AAP (i.e., 19%) received an ASMR V or a mix of ASMR V or no reimbursement.

Conclusions

- In the first year since the reform, the ATU reform does not appear to have significantly impacted early access. There is still some reluctance from the authorities to restrict patient access to life-saving treatment, as shown by HAS granting AAP to products rejected by the TC.
- This study shows that the need for comparative data remains the main driver for positive AAP advice from the TC and that lack of such data is likely to lead to rejection. These criteria are consistent with reimbursement decisions, ASMR and SMR ratings later on.
- As with every reform that takes a 'one-size fits all' approach, the reform did not address the limitations of the previous system. Specifically, rare diseases still do not have exemption for evidence requirements, and the lack of familiarity in primary care can still limit uptake[9].
- Despite its limitations, the AAP does remain an attractive programme, and can also be seen as an indicator of future TC reimbursement ratings as demonstrated in this study.
- President Macron, who drove the July 2021 ATU reform, promised to put in motion reforms on health care as part of his manifesto[10]. Could it be already time to adapt the AAP system?

Abbreviations: ATU – Autorisation Temporaire d'Utilisation; FSSL – Loi de financement de la sécurité sociale; AAP – Autorisation d'accès précoce; EPR – European Pharmaceutical Review; HAS – Haute Autorité de Santé; SoC – standard of care; TC – Transparency Commission; MoA – mechanism of action

Sources: 1. LOI n° 2020-1576 du 14 décembre 2020 de financement de la sécurité sociale pour 2021. (2020), Legifrance.gouv.fr.; 2. Matthews, C., Stefani, S., Urruticoechea, P. (2021), France's temporary authorisation (ATU) programme: reform implications; 3. Haute Autorité de Santé (2022), Autorisation d'accès précoce aux médicaments : un premier bilan positif et des principes d'évaluation affinés; 4. Haute Autorité de Santé (2021), Avis sur les médicaments – Abecma; 5. Haute Autorité de Santé (2021), Avis sur les médicaments - Opdivo & Yervoy; 6. Haute Autorité de Santé (2022), Avis sur les médicaments – Gavreto; 7. Haute Autorité de Santé (2021), Avis sur les médicaments – Kimozo; 8. Haute Autorité de Santé (2021), Avis sur les médicaments – Rybrevant; 9. Rosier, F. (2022), Le Monde; 10. Politics desk (2022), Le Monde

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