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Italian Council of State Improves Access to Investigational Medicines

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Recently, the Council of State (*i.e.*, the *Italian* supreme administrative court and consultative body) adopted an important advisory opinion, which allows for improved access to investigational medicines by patients in Italy. In particular, the Council of State found that patients may be enrolled in compassionate use programmes or supplied with a medicine listed in the so-called 648 List after the product has obtained a marketing authorization, at least until the company starts to commercialize it in Italy. The latter normally presupposes that the product is classified as subject to reimbursement.

Access to Medicines Not Authorized in Italy

There are *de facto* two regimes allowing patients to access investigational medicines (*i.e.*, medicines that are not yet authorized in Italy).[1] The first, applied in most cases, is the compassionate use regime. The second, used in more exceptional cases, is the so-called 648 regime. The two regimes may not be applied simultaneously.

Compassionate Use: the compassionate use of medicinal products is regulated by Decree of the Ministry of Health on the Therapeutic Use of Medicinal Products Subject to Clinical Research of 8 May 2003 (Decree of 2003). The Decree allows pharmaceutical companies to supply, free of charge, a medicine that is not authorized in Italy where there is no alternative therapy available for the treatment of serious diseases, rare diseases or medical conditions that are life-threatening.

Recent examples of medicines supplied through the compassionate use route are sofosbuvir and nivolumab.

Reimbursement Under the 648 Regime: Law 648/96 permits the supply and reimbursement of products that do not have a marketing authorization under certain conditions. In particular, the Law empowers the Italian Medicines Agency (AIFA) to list a product in the so-called “648 List” (as subject to reimbursement) if there is no valid therapeutic alternative, and (i) the product has obtained a marketing authorization in other countries but not in Italy; (ii) the product is subject to clinical research but it is not yet authorized in Italy; or (iii) the product’s use is for an indication other than that authorized in Italy. Formally, a request to include a product in the 648 List may not come from the pharmaceutical company supplying the product.

AIFA has sometimes used the 648 route to allow patients to have access to an investigational medicine after the end of a compassionate use programme. For example, upon termination of the compassionate use programme for nivolumab the product was included in the 648 List until its commercialization.

The Interplay Between Access to Investigational Medicines and Pricing and Reimbursement

In principle, once a product is authorized (in Italy or centrally) it may not be supplied to patients through compassionate use programmes or the 648 route. This is because both the Decree of 2003 and Law 648/96 require that the products supplied be "not authorized." AIFA, and now the Council of State, take a broad view of this and consider that it *de facto* means that the product is non-marketable in Italy.

All medicinal products must have a pricing and reimbursement status in order to be placed on the Italian market. After obtaining a marketing authorization, most products are automatically classified as non-reimbursed under Class C(nn) (*i.e.*, the class of non-reimbursed products pending reimbursement evaluation). The placement of a product in such class allows the marketing authorization holder (MAH) to immediately market (and advertise) the product as a non-reimbursed product provided that the MAH notifies its price to AIFA before it starts sales. If the MAH intends to seek reimbursement, it must submit a specific request to AIFA and negotiate the reimbursed price with the agency. However, the Italian rules on pricing and reimbursement normally allow companies to submit such request only after the product has obtained a marketing authorization.

In practice, this may lead to situations where, pending the negotiation on the reimbursement status of a product (which often lasts for over one year), the product is neither available to patients via compassionate use or 648 routes, nor through the ordinary commercial channels.

The Council of State's opinion tries to remedy this situation by allowing AIFA to omit the listing of products in Class C(nn) upon marketing authorization. This allows for compassionate use programmes or inclusion on the 648 list until the medicine is commercialized in Italy.

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[1] For the sake of completeness, there is also a specific regime (*i.e.*, Law 94/98 — so-called "Di Bella" Law) that allows physicians to prescribe a product off-label for individual patients, but we will not discuss it today.

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