AIFA Assessments of Requests for Inclusion in 648/96 LIST: an update (January 2017 to June 2021)

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INTRODUCTION/BACKGROUND

Law n. 648 of 23rd December 1996 regulates early access, reimbursed by NHS, to medicinal products for a cohort of eligible patients according to specific criteria, where a valid therapeutic alternative is not available.

It is possible to submit an inclusion request into 648 list for:

- innovative medicinal products authorized in other countries, but not in Italy;
- medicinal products not yet authorized, but undergoing clinical trials;
- medicinal products to be used for a therapeutic indication different from the authorized one.

In all cases, it is requested that at least Phase II studies are completed, demonstrating adequate efficacy with an acceptable risk profile related to the specific therapeutic indication.

Pursuant to art. 3 Law 79/2014, inclusion into 648 list is possible also when a valid therapeutic option is available, for an indication known and consistent with research conducted nationally and internationally, following criteria of economicity and appropriateness.

The request can be submitted by patient associations, scientific societies, health authorities/hospitals, universities, physicians; it may also be evaluated based on AIFA Technical Scientific Committee (CTS)'s recommendation.

The CTS is responsible for evaluation of the requests; upon a positive CTS opinion, medicinal products are included in the 648/96 list for the evaluated therapeutic indication. The 648/96 list is published on the AIFA website and regularly updated.

OBJECTIVES

The aim of this analysis is to investigate the CTS assessment outcome and approach in the evaluation of applications for inclusion of a new active substance/therapeutic indication in the Law 648/96 list in the timeframe January 2017 - June 2021.

METHODS

Data were extrapolated from an internal database (DB), which collects all CTS assessment outcomes as available on the AIFA website.

The analysis was focused on all requests submitted to AIFA from January 2017 to June 2021 and evaluated for the first time by CTS, broken down by year and by therapeutic area (rare diseases, rare tumors, other oncology indications, and other indications). A specific focus was dedicated to ATMPs.

A sub-analysis investigating the duration of AIFA assessment was performed on the completed procedures, measured from the first time the application for inclusion appeared in the CTS meeting agenda, to the date of conclusion of the procedure, defined as the CTS meeting date in which a positive or negative opinion was expressed by CTS.

RESULTS

From January 2017 to June 2021, a total of 249 applications were assessed by CTS, of which 209 were new applications. Among these, 42 (20.1%) concerned rare diseases, 28 (13.4%) rare tumors, 51 (24.4%) other oncology indications, and 88 (42.1%) involved other indications. (Figure 1)

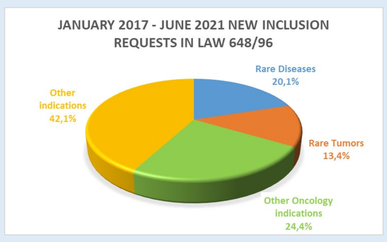

Figure 1- New inclusion requests in Law 648/96 by therapeutic area

During the considered timeframe, CTS approved 93 (44.5%) requests; 107 requests (51.2%) were rejected, and 9 (4.3%) were still ongoing at the analysis cut-off date (30th June 2021).

An analysis of the outcomes issued by CTS shows a similar percentage of positive opinions for three areas (other oncology indications, rare tumors and other indications - respectively 53%, 50% and 45%); while for rare diseases, a much lower percentage of positive opinions was recorded (29%) (Figure 2).

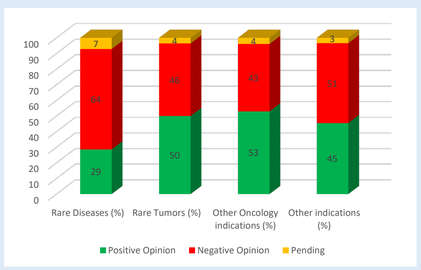

Figure 2 - New requests for inclusion in Law 648/96 list; outcomes by therapeutic area

In 2020, new requests for inclusion submitted to CTS assessment almost doubled (64) vs the previous years (38, 35 and 38 requests assessed respectively in 2017, 2018 and 2019); this appears not to be related to requests for COVID-19 treatments, since only 5 requests for this indication were assessed in 2020, and 2 in Jan-June 2021). The majority of requests submitted in 2020 (39; 61%), was for "other indications".

Also, the majority of requests were evaluated in the first semester (48/64), thus confirming that the increase wasn't related to COVID-19 infection.

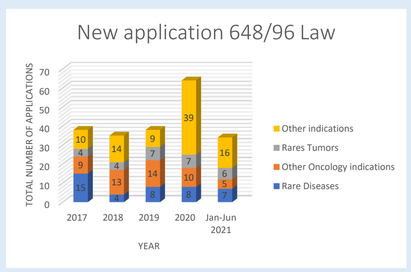

Figure 3 - New inclusion applications evaluated by CTS by year and therapeutic area

Analysing CTS outcomes by year of submission, we observed a progressive reduction in the percentage of positive opinions from 2017 to 2021 . Up to 2019, the percentage of positive opinions exceeded the percentage of negative opinions (53% vs 45% in 2017, 57% vs 43% in 2018 and 47% vs 45% in 2019). On the contrary, in 2020 there were more negative opinions (63% vs 33% of positive opinions) and it was the same in the first half of 2021 (53% of negative opinions vs 41% of positive opinions) (Figure 4).

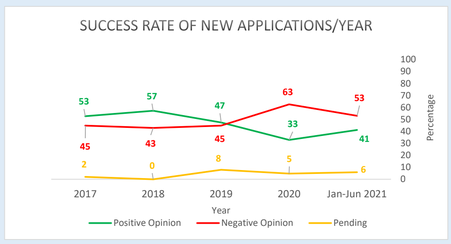

Figure 4 - Success rate of 648 applications

The analysis shows that, for rare diseases, negative opinions always exceeded (or were equal to, in 2019 only) positive opinions; in the first half of 2021, no rare disease requests were approved out of 7 evaluated. The situation was partially better for rare tumors until 2019; however, in 2020 and 2021 the trend was inverted, and in the first half of 2021, only one out 6 applications was approved (Figure 5). In general, non-rare indications have a higher percentage of success than rare indications (Figure 3, Table 1).

Figure 5- Number of positive and negative opinions by year and therapeutic area

The sub-analysis of the evaluation timeline performed on the procedures assessed by CTS from January 2017 to June 2021, showed that 143 (69%) requests were assessed by CTS during one meeting. Analyzing their distribution by therapeutic area, it was observed that the requests concerning other oncology indications are assessed more quickly (highest percentage -78%- of evaluation in only one meeting) (Table 1).

Fifty-seven (27%) of the 209 applications analyzed were assessed in more than 1 meeting. Nine applications (4%) were still under evaluation at cut off date.

Considering the applications evaluated in more than one CTS meeting, the duration of the CTS evaluation was in average 125 days, with a median of 40 days and a range of 15-548 days. The assessment of the requests belonging to the rare area (rare diseases and rare tumors) took the longest evaluation with a time average of 155 days and 146 days and a median of 64 days and 120 days respectively (Table 1).

In general, there was a highest success rate in the applications evaluated in more than one CTS meeting (53% vs 44%). This is marked in the rare tumors where the percentage of positive opinions ranges from 41% in the applications evaluated in a single meeting against 70% among the applications evaluated in several meetings. Same situation in rare diseases (22% vs 44%) (Table 1).

Table 1- Time of evaluation by area and outcome from January 2017 to June 2021

	Total		Rare Diseases		Rare Tumors		Other Oncology indications		Other indications	
Applications evaluated	**209**		**42**		**28**		**51**		**88**	
Evaluation ongoing	9 (4%)		3 (7%)		1 (3%)		2 (4%)		3 (3%)	
Applications evaluated in one CTS meeting	**143 (69%)**		**23 (55%)**		**17 (61%)**		**40 (78%)**		**63 (72%)**	
CTS opinion outcome (n, %)	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
	63 (44%)	80 (56%)	5 (22%)	18 (78%)	7 (41%)	10 (59%)	22 (55%)	18 (45%)	29 (46%)	34 (54%)
Applications evaluated in > 1 CTS meetings	**57 (27%)**		**16 (38%)**		**10 (36%)**		**9 (18%)**		**22 (25%)**	
Average duration of evaluation (days)	125		155		146		136		63	
Median duration of evaluation (days)	40		64		120		36		36	
CTS opinion outcome (n, %)	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
	30 (53%)	27 (47%)	7 (44%)	9 (56%)	7 (70%)	3 (30%)	5 (56%)	4 (44%)	11 (40%)	11 (50%)
Average Time (days) by outcome	139	88	256	76	167	98	173	89	32	94
Median Time (days) by outcome	40	49	267	49	146	92	36	27	36	36

ATMPs – ATMPs deserve a specific focus, given their innovativeness and potential high impact for patients.

From January 2017 to June 2021, only three requests for ATMPs were evaluated: Zalmoxis in 2018, Zolgensma in May 2020 and Libmeldy in November 2020; only Zolgensma received a positive opinion, in September 2020, after 126 days of evaluation (Table 2).

Table 2-ATMPs evaluated from January 2017 to June 2021

	First CTS evaluation	Final CTS evaluation	Duration of evaluation	CTS opinion
Libmeldy	11/11/2020	11/01/2021	2 meetings – 61 days	Negative
Zalmoxis	29/10/2018	29/10/2018	1 meeting	Negative
Zolgensma	13/05/2020	16/09/2020	2 meetings -126 days	Positive

CONCLUSIONS

From January 2017 to June 2021, 209 new applications for inclusion in Law 648/96 were assessed by CTS. A clear trend was observed towards the reduction of positive opinions, ranging from a maximum 57% in 2018 to 33% in 2020.

The highest number of requests was recorded in 2020. The increase was observed in particular for "other indications"; however, this doesn't seem to be related to pandemic situation, since only 5/64 requests concerned treatments for COVID-19.

Across the analyzed timeframe, 69% of the applications were evaluated in one CTS meeting, with a success rate of 44%; in particular, the requests related to other oncology indications had a highest percentage of assessments in only one meeting, with a success rate of 55%.

The chance of success seems to increase when the application is evaluated in more than one CTS meeting (53% vs 44%); in certain cases (3 out of 11), this may be explained by counterarguments presented by the applicants, which may allow to change the initial negative assessment.

Finally, the lowest percentage of positive opinions was recorded for rare diseases (29%) where it was observed also that the evaluations, regardless of the outcome, required the longest assessment process. This is quite surprising since rare diseases would seem to represent an ideal setting for the application of Law 648/96, as very often no valid therapeutic alternative is available for these diseases. Budget constraints might be contributing to explain these results; however, a reflection is needed from regulators, because the unmet need in rare diseases remains, in many cases, unanswered.

AIFA https://www.aifa.gov.it/web/guest/legge-648-96 Last access: 7th October 2021