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THE ECONOMICS OF ORPHAN DRUGS: THE CASE OF OSTEOSARCOMA TREATMENT *

Stefano Capri[**]

Orphan drugs and economic evaluation

In the last report on orphan drugs published by the European Union the listed orphan drugs with market authorization are about 64 (Orphanet Report Series - List of Orphan Drugs in Europe. October 2010). In 2008, fourteen applications have been submitted for orphan medicinal products; seven have received a positive opinion and two a negative opinion; six sponsors have withdrawn their application before getting the opinion. The European Commission has granted five market authorizations. (Committee for Medicinal Products for Human Use. December 2008 Plenary Meeting, Monthly Report. In: EMEA, editor.; 13 January 2009). By consequence the spending for these treatments increased, then the health authorities started using economic evaluation criteria already in place for not orphan drugs.. However, to apply the methods of economic assessment to the orphan drugs, ultimately the budget impact analysis but also the cost-effectiveness analysis, present problems in terms of method and application (Drummond MF, Wilson DA, Kanavos P et al. Assessing the economic challenges posed by orphan drugs. International Journal of Technology Assessment in Health Care, 23:1 (2007), 36–42).

Firstly, the prices and the corresponding cost-effectiveness estimates are high for orphan drugs. This is basically because, compared to the high costs in R&D, the profitability of this products is scarce, due to the rarity of the disease. Therefore, on a patient per patient basis, the ICER is usually very high (see here the Discussion).

On the other hand, because of the small number of patients suffering from rare diseases, it very difficult to enroll patients to make the randomized controlled trials powered to get the clinical data needed to demonstrate the efficacy of these drugs . In short, the standard economic evaluation procedures applied to orphan drugs often result in very poor cost-effectiveness ratios.

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Considering the UK context, probably the most advanced in this kind of appraisals, the range of ICER for approved orphan drugs if very large, ranging from £ 23,000 to £391.000 for QALY gained (Table 1).

Table 1. ICER values of some ultra-orphan drug in current use in UK

Product	Condition	Prevalence	Preliminary estimated ICER (£ per QALY)
Agalsidase beta (Fabrazyme)	Fabry's	200	203,009
Imiglucerase (Ceredase)	Gaucher's (types I and III)	270	391,244
Laronidase (Aldurazyme)	Mucopolysaccaridosis (type 1)	130	334,880
Miglustat (Zavesca)	Gaucher's (type I)	270	116,800
Nonacog alfa (BeneFIX)	Haemiphilia B	350	172,500
Iloprost (Ventavis)	Primary pulmonary hypertension	100	23,324

(NICE. Appraising Orphan Drugs 2006)

Table 2: Resource Costs

Resource	Cost 2009 (€)	Reference
Second line Chemotherapy	2,013	Informatore Farmaceutico 2009
Central line insertion	5,855	Converted from UK cost using conversión rate from Jan 2008 and uplifting to 2009 using Italian Consumer Price Index
CT scan	138	Tariffario prestazioni ambulatoriali Regione Lombardia 2009
Bone Isotope Scan	138	Tariffario prestazioni ambulatoriali Regione Lombardia 2009
Outpatient visit for MIFAMURTIDE treatment	21	Tariffario prestazioni ambulatoriali Regione Lombardia 2009
Outpatient visit – No treatment	55	Clinical Opinion
MRI Scan	272	Tariffario prestazioni ambulatoriali Regione Lombardia 2009
NHS paliative care	4,239	Di Cosimo S, Pistillucci G, Ferretti G et al. Palliative home care and cost savings: encouraging results from Italy. NZMJ 14 March 2003, Vol 116 No 1170.
Cost of Hearing AE	285	Converted from UK cost using conversión rate from Jan 2008 and uplifting to 2009 using Italian Consumer Price Index
Cost of Infusion reaction	10	Informatore Farmaceutico 2009, 20 tablets, 500mg = €2. 100 tablets, 500mg = €10
Non-pulmonary surgery	3,979	DRG Regione Lombardia 2009, DRG 239 Pathologiccal Fractures or Malignancy of Bone and Connective Tissue
Pulmonary surgery	4,282	DRG Regione Lombardia 2009, DRG 78 Pulmonary Embolus
Annual cost of amputation	5,594	DRG Regione Lombardia 2009, DRG 13 Amputation
Annual cost of endoprosthesis	5,510	DRG Regione Lombardia 2009, Average value of DRG 210-211, hip replacement with and without CC

NICE, which is already taken as a reference all around the national health authorities, at least in terms of basic orientation, recently suggested some "guidelines" regarding the economic evaluation of orphan drugs (NICE. Appraising Orphan Drugs 16 March 2006). Althought this document is still on progress, the main conclusions are the following: 1) indicative ICERs for ultra-orphan products are a ten-fold increasing their threshold values compared to the decision rules currently applied in conventional appraisals; 2) the implicit benchmark for orphan drug should be the ICER of the already marketed orphan drug; and 3) the final cost per QALY should not be weighed by equity parameters.

Also the Australian health authorities made some distinction when appraising orphan drugs (George B, Harris A, Mitchell A. Cost-effectiveness analysis and the consistency of decision making: Evidence from pharmaceutical reimbursement in Australia (1991 to 1996). Pharmacoeconomics.2001;19:1103-1109). In particular, they focus the attention, beyond the uncertainty surrounding the cost-effectiveness themselves, other factor as the severity of the disease, the availability of alternative therapies to treat the disease and the cost to be faced by the patient in case the drug is not listed for public reimbursement, which arise also the point of equity. This is the reason way in Australia the Commonwealth Government provides funds under a specific appropriation outside the Pharmaceutical Benefits Scheme, with the specific purpose to support the access to these expensive and lifesaving drugs (Commonwealth of Australia. Other supply arrangements outside the Pharmaceutical Benefits Scheme (PBS). Department of Health and Ageing, 2006).

According one of the first studies on equity and orphan drug (Ubel PA, DeKay ML, Baron J, et al. Cost-effectiveness analysis in a setting of budget constraints-is it equitable? N Engl J Med. 1996;334:1174-1177), policy makers appear to allocate resources to all patients suffering from a disease, irrespectively of the cost- effectiveness of treatment. This finding explains the tendency to reimburse ineffective treatments for rare diseases or small groups, and at the same time the tendency not to reimburse some treatments with high budget impact.

In economics terms, the question is how much efficiency (in terms of maximizing health gain from the healthcare budget) the society is willing to trade for more equity (in giving therapy to whome currently the access is denied).

There is still an unmet need for intensified research into health economic evaluation models beyond cost-effectiveness analysis. These should address the above-mentioned aspects including price volume trade-offs, hereby better addressing the realities of new drug development and the information needs of policy-makers (M. Schlander and M. Beck. Expensive drugs for rare disorders: to treat or not to treat? The case of enzyme replacement

therapy for mucopolysaccharidosis VI. Current Medical Research and Opinion, vol. 25, no. 5, 2009, 1285–1293).

The ethical issue is out of the scope of the present study, however through the discussion concerning the available tools of the economic evaluation, we think that valuing health outcome more highly for rare conditions is incompatible with other equity principles and theories of justice, mainly because it may impose substantial and increasing costs on the healthcare system. Moreover, the costs will be borne by other, unknown patients suffering from more common diseases, who will be unable to access effective and cost effective treatment as a result (Christopher McCabe, Karl Claxton, Aki Tsuchiya. Orphan drugs and the NHS: should we value rarity? BMJ 2005;331:1016–9).

It is well recognized that spending public resources on one health programme reduces the resources potentially available for other health programmes, expecially in a context where budget constraints exist, therefore it would be an unethical to take a decision which is not supported by any economic evaluation (Raftery J. NICE and the challenge of cancer drugs. BMJ 2009;338:b67.). Nevertheless ICER threshold values are insufficient for assessing the value for money of any intervention, particularly in the rare disease context where equity plays a primary role in the decision making of health authorities (Cleemput I, Neyt M, Thiry N et a. Using threshold values for cost per quality-adjusted life-year gained in healthcare decisions. International Journal of Technology Assessment in Health Care, 27:1 (2011), 71–76).

The present economic evaluation might help the decision makers in improving the transparency of the resources allocation process.

Finally, when it can be shown that an orphan drug is cost-effective, with an higher ICER compared to the threshold accepted for standard drugs, but anyhow lower compared to the vaste majority of the other orphan drugs, then this should encourage the R&D investments in rare diseases (Weinstein MC. The cost-effectiveness of orphan drugs. Am J Pub Health 1991;4:414-415)

Orphan drug in the treatment of osteosarcoma

Osteosarcomas are rare tumors. Approximately 750 to 900 new cases are diagnosed each year in the United States, of which 400 arise in children and adolescents younger than 20 years of age (Gurney, JG, Swensen, AR, Bulterys, M. Malignant bone tumors. In: Cancer Incidence and Survival Among Children and Adolescents: United States SEER Program 1975-1995 (Pub #99-4649), Ries, LA, Smith, MAS, Gurney, JG, et al (Eds). SEER program, National Cancer Institute, Bethesda, MD 1999. p.99-110. Data from the American Cancer Society, http://www.cancer.org/docroot/home/index.asp, 2009). Despite their rarity, osteosarcomas are

the most common primary malignancy of bone in children and adolescents and the fifth most common malignancy among adolescents and young adults aged 15 to 19 (Smith, MA, Gurney, JG, Ries, LA. Cancer in adolescents 15 to 19 years old. In: Cancer Incidence and Survival Among Children and Adolescents: United States SEER Program 1975-1995 (Pub #99-4649), Ries, LA, Smith, MAS, Gurney, JG, et al (Eds). SEER program, National Cancer Institute, Bethesda, MD 1999. Stiller CA, Bielack SS, Jundt G, Steliarova-Foucher E. Bone tumours in European children and adolescents, 1978-1997. Report from the Automated Childhood Cancer Information System project. Eur J Cancer. 2006;42(13):2124-35).

The classic osteosarcoma is rare (0.2% of all malignant tumours) with an estimated incidence in Italy of 3 cases/million population/year. (Picci P. Osteosarcoma (Osteogenic sarcoma). Orphanet Journal of Rare Diseases 2007, 2:6 doi:10.1186/1750-1172-2-6)

Osteosarcoma is the most common primary bone. Lesions are usually seen in the long bones, rarely in the soft tissues, and are highly aggressive, with a propensity to metastasise particularly to the lung in the early disease stages. If left untreated, the primary lesion will undergo local and systemic progression leading to death within a matter of months, usually as a result of respiratory failure.

Due to the high frequency of micro-metastases in osteosarcoma in about 85-90% of patients the surgical treatment alone usually fails.

In the last 25 years the therapeutic approach combining pre and post-operative chemoterapy to the radical surgical treatment dramatically improved the overall survival rate.

A new drug, Mifamurtide (mifamurtide, liposomal muramyl tripeptide phosphatidyl ethanolamine) has been approved and recommended for the treatment of osteosarcoma.

The largest study ever completed in osteosarcoma, enrolling approximately 800 patients, showed that the addition of Mifamurtide to the post –operative chemotherapy resulted in improvement in 6-year overall survival from 70% to 78%, which is an almost one third reduction in the risk of death (Meyers, PA, Schwartz, CL, Krailo, MD, et al. . The Addition of Muramyl Tripeptide to Chemotherapy Improves Overall Survival-A Report From the Children's Oncology Group. Journal of Clinical Oncology 2008; 26 633-638.)

Mifamurtide is indicated in children, adolescents and young adults for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection. It is used in combination with post-operative multi-agent chemotherapy. Safety and efficacy have been assessed in studies of patients 2 to 30 years of age at initial diagnosis.

Since Mifamurtide is indicated for use as an add-on treatment to 3- or 4-agent adjuvant chemotherapy, the comparator treatment used for assessment of the decision problem is a 3- or 4-agent chemotherapy regimen alone, which represents the current standard treatment approach.

Economic evaluation of the orphan drug

Model

The cost-effectiveness of Mifamurtide as add-on treatment to standard chemotherapy for the high grade resectable non metastatic osteosarcoma, compared to standard chemotherapy alone has been evaluated by using a Markov model[1].. In order to reflect the Italian setting, the model has been adapted and modified according to local clinical practice and resources consumption pathways.

The basic structure of the model is funded on the on the 12.25-year phase 3 study, a prospective randomized clinical trial of treatment of newly diagnosed patients suffering from high grade resectable non metastatic osteosarcoma, where Mifamurtide as add on treatment to standard chemotherapy was compared to the standard chemotherapy alone in terms of overall survival.

(Meyers, PA, Schwartz, CL, Krailo, MD, et al. . The Addition of Muramyl Tripeptide to Chemotherapy Improves Overall Survival-A Report From the Children's Oncology Group. Journal of Clinical Oncology 2008; 26 633-638.).

The Markov model structure includes 6 primary states and the probability of transition between the health states for the first 12.25 years is based on data derived from the phase III clinical trial and the clinical literature (Meyers, 2008).

The states included in the model, all defined according to the post-treatment maintenance phase of the study, are: disease free, disease progression, recurrence, post recurrence- disease free , post recurrence – disease free and death.

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[1] The model was originally developed by Chris Knight at RTI-HS, then converted from TreeAge® version of the model into Microsoft® Excel.

Figure 1: Model Structure
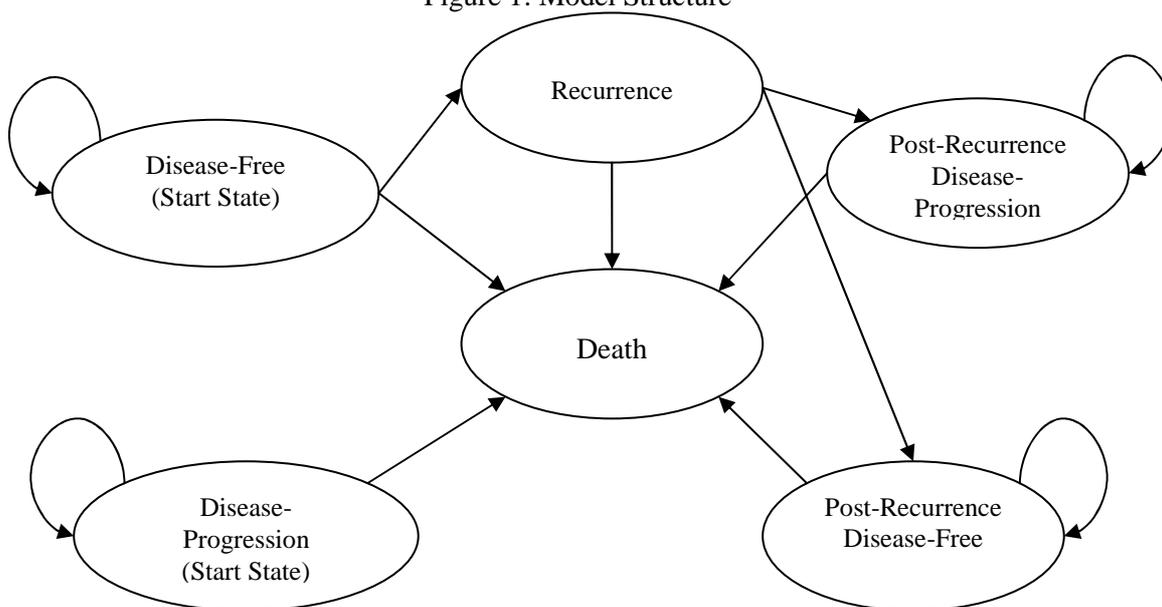
The Markov time-cycle is 6 months except for the first cycle which is 9 months. The first cycle is 9 months to reflect the fact that all chemotherapy and Mifamurtide infusions occur over the first 36 weeks, according to the protocol study .

Since Mifamurtide is addressed to a young population supposed to have a long life expectancy, it is appropriate to consider a time horizon in the analysis beyond the 12.25 year trial period, up to a total of 60 years. Concerning the costs and clinical outcomes of the remaining patients within each health state at the end of 12.25 years, the model made two main assumptions. The first assumption is that patients within the disease-free state at 12.25 years are assumed to have a mortality rate equivalent to the general population. The second one is that patients within the post-recurrence disease-free state are assumed to have a mortality rate dependent on the time to recurrence.. For patients who have a recurrence within 2 years, the 6-monthly mortality rate is 14.87%. For patients who have a recurrence after 2 years, the 6-monthly mortality rate is 4.98%. (Ferrari S, Briccoli A, Mercuri M, Bertoni F, Picci P, Tienghiet A al. Post relapse Survival in Osteosarcoma of the Extremities: Prognostic Factors for Long-Term Survival. J Clin Oncol. 2003; 21:710-715)

The mortality rate of post-recurrence disease-free patients can be altered to equal the general population after a given time period. Thus, post-recurrence disease-free patients can have the same mortality risk as those of disease-free patients if they remain disease-free for a given time period (default: 5 years). Introducing this parameter option is investigated in the sensitivity analysis.

The base case results included also the following additional assumption: no amputation or limb salvage costs; hearing loss adverse events not included; discounting rates of 3% for both costs and outcomes applied.

Efficacy

The efficacy data of Mifamurtide has obtained from the phase III (INT 0133 trial) assessing the use of Mifamurtide as an add-on to multi-agent chemotherapy in children, adolescents and young adults with osteosarcoma (Meyers, PA, Schwartz, CL, Krailo, MD, et al. . The Addition of Muramyl Tripeptide to Chemotherapy Improves Overall Survival-A Report From the Children's Oncology Group. Journal of Clinical Oncology 2008; 26 633-638.).

This 12-year study, a prospective randomized trial, compared Mifamurtide as add on treatment to standard chemotherapy versus the standard chemotherapy alone (a regimens consisting of cisplatin, doxorubicin and methotrexate ± ifosfamide) to determine whether the addiction of Mifamurtide could enhance overall survival (OS) in these patients.

The overall survival data showed that the addition of Mifamurtide to chemotherapy significantly enhanced overall survival compared with chemotherapy alone. For the intention-to-treat population, the hazard ratio for death was 0.72 (95% CI: 0.53 to 0.97; p=0.0313) at a median follow-up of 7.9 years corresponding to a 28% relative reduction in overall mortality.

After a median follow up of 7.9 years the addition of Mifamurtide to multi-agent chemotherapy increased overall survival (hazard ratio, 0.72; 95% CI, 0.53 to 0.97; p=0.0313) and disease-free survival (hazard ratio, 0.78; 95% CI, 0.61 to 1.01; p=0.0586) in patients (less than 30 years age) with high grade, resectable, non metastatic osteosarcoma compared with chemotherapy alone.

The results from the trial showed that there were differences between the two treatment arms in relation to the proportion of patients starting in the disease-free state. Having a difference between the treatment arms in the number of patients starting in each state is not appropriate when trying to compare the difference in clinical outcome between the two treatments. Thus, as a default assumption, the model considers that 100% of patients start in the disease-free health state, then consequently the efficacy has been proportionally applied to the two groups of patients.

Costs

As far as resources concern, the consumption of drugs has been established based on the clinical trials (see the following paragraph), taking the unit costs of each drug from the Official Italian Drug Formulary (Informatore Farmaceutico, 2009). Palliative care has been estimated

from an Italian study in one hospital Division of Oncology with 550 cancer patients followed for a period of 20 months (Di Cosimo S, Pistillucci G, Ferretti G et al. Palliative home care and cost savings: encouraging results from Italy. NZMJ 14 March 2003, Vol 116 No 1170); the values has been inflated with the Consumer Price Index. Visits, diagnostic procedures and ambulatory treatments are based on Public Tariffs (Tariffario prestazioni ambulatoriali Regione Lombardia 2009), whether hospital procedures are valued with DRGs Tariffs (DRG Regione Lombardia 2009). Since the cost of the central line inserction and the hearing adverse event were not available, the UK costing has been converted in euros and inflated to 2009 using the Consumer Price Index. The cost estimates for the resources used in the CE model are shown in Table 2 and the cost of the drug treatments are summarized in table 3.

Table 3: Cost of the drug treatments

Parameter	Value	Source
Cost of adjuvant chemotherapy regimen A	€35,692	Informatore Farmaceutico 2009
Cost of adjuvant chemotherapy regimen B	€42,065	Informatore Farmaceutico 2009
Cost of MIFAMURTIDE dose	€2.890	Price of new product approved by AIFA

Note: Regimen A maintenance therapy consisted of four doses of doxorubicin ($25mg/m^2$/day over 72 hours), two doses of cisplatin ($120mg/m^2$) and eight doses of methotrexate ($12g/m^2$).Regimen B maintenance therapy consisted of four doses of doxorubicin ($25mg/m^2$/day over 72 hours), four doses of cisplatin ($120mg/m^2$), three courses of ifosfamide ($1.8g/m^2$/day x 5 days) and eight doses of methotrexate ($12g/m^2$).

Cost are expressed in 2009 Euros.

Number of doses and extra outpatient visits

The expected number of Mifamurtide doses to be administrated to each patient is 48, according to the standard indication. However, it was clear from the National Institute of Clinical Excellence (NICE) Final Single Technology Appraisal and the clinical trial report that there was a large variation in the number of Mifamurtide doses the patients received. Table 4 shows the patient distribution of the number of Mifamurtide doses patients received together with the average number of Mifamurtide doses the patients received. As the efficacy data is based on the number of actual Mifamurtide doses administered and not the assumed 48 doses, the model default is the actual average of Mifamurtide doses administered i.e. 38.4.

Table 4: Mifamurtide dosing for patients receiving adjuvant therapy

Number of Doses	Mid-Point	Percentage of Patients
>50	53	1.7%
46-50	48	51.7%
41-45	43	10.2%
36-40	38	7.4%
31-35	33	4.0%
26-30	28	5.1%
21-25	23	6.3%
16-20	18	2.8%
11-15	13	2.9%
6-10	8	3.4%
1-5	3	4.5%
Average number of MIFAMURTIDE doses administered		38.4

Source: Based on Phase III actual Mifamurtide Dosing. Weighted average calculations exclude zero dose patients.
IDM NICE submission data prepared by Pricespectives; BRANDominance analysis.

Based on clinical advice, 30% of extra outpatient attendances are needed in the administration of Mifamurtide over and above the number of outpatient attendances associated with the maintenance chemotherapy was applied. In other words, it is estimated that 30% of Mifamurtide doses would require the patient to make an extra outpatient attendance visit as the dosing could not be undertaken at the same time as part of the maintenance chemotherapy.

The two regimen induction chemotherapies occur over a 20-24 week timeframe in which, with double dosing for the first 12 weeks, 32 doses of Mifamurtide are administrated. Therefore, it was felt that extra outpatient attendances should only be applied to Mifamurtide doses in excess of 32 doses. Table 5 shows that additional outpatient attendances needed for the number of Mifamurtide doses administered together with the average number of additional Mifamurtide outpatient attendances required based on the actual patient distribution of Mifamurtide doses received shown in Table 4.

Table 5: Number of Additional Outpatient Visits for Mifamurtide Doses

Number of Doses	Additional Outpatient Visits
>50	17
46-50	12
41-45	7
36-40	2
31-35	0
26-30	0
21-25	0
16-20	0
11-15	0
6-10	0
1-5	0
Average number of Mifamurtide Outpatient attendances	7.4

As alternative approach, a detailed analysis of the dosing timings undertaken in the trial for the administration of the maintenance chemotherapy and adjuvant Mifamurtide therapy shows that the additional outpatient attendances required for the administration of Mifamurtide may be actually higher than originally thought. Taking chemotherapy regimen B, we can calculate the number of times that Mifamurtide was administered alone and thus conclude when an additional outpatient attendance would have been required. For example, if a patient only received the first 13 doses of Mifamurtide then 7 additional outpatient attendances would be required.

Adopting this approach, Table 6 shows an alternative number of 22.7 additional outpatient attendances required to administrate Mifamurtide doses base on the actual patient distribution of the number of Mifamurtide doses patients received.

Table 6: Alternative Number of Additional Outpatient Visits for Mifamurtide Doses

Number of Doses	Additional Outpatient Visits
>50	34
46-50	29
41-45	24
36-40	21
31-35	17
26-30	15
21-25	13
16-20	11
11-15	7
6-10	5
1-5	3
Average number of Mifamurtide Outpatient attendances	22.7

The differences in additional outpatient attendances required for the administration of Mifamurtide is investigated in the sensitivity analysis.

Utility Values

The default health related quality of life (HRQoL) utility values applied to each of the health states are shown in Table 7.

The cost-effectiveness model has the ability to apply age-related utility weights to the health state utilities and these are derived from the UK Population Norms for EuroQol Group 5-Dimension Self Report Questionnaire (EQ-5D) for Kind et al. (1999) (Kind P, Hardman G, Macran S. UK Population Norms for EQ-5D. Centre for Health Economics Discussion paper 172. University of York, 1999) however there is no Italian alternative. The age-related utility weights are not a default assumption and thus the effect of not updating to country specific values is negligible. The specific value for the five health state (plus the death) were derived from the Nice HTA review of Mifamurtide (Table 7).

Table 7: Health State Utility Values

Health State	Value	Source
Disease Progression	0.39	NICE HTA review. The HTA review provided an estimate of 0.44 for the disease progression to death category, which was adjusted by the -12% correction factor as above.
Disease Free	0.75	EQ 5D survey. This value is supported by a study in 31 survivors of childhood bone tumours which also reported a value of 0.75 using the HUI3 instrument (Alessi et al. 2007).
Recurrence	0.61	NICE HTA review. The HTA review provided an estimate of 0.69 for disease-progression/recurrence category. A correction factor of -12% was applied based on the ratio for the average utility for disease-free state in the EQ 5D survey and Alessi et al. 2007 (0.75) and the disease-free category in the NICE HTA review (0.85).
Disease Free post recurrence	0.75	Assumed to be the same as disease-free value.
Disease Progression post recurrence	0.39	Assumed to be the same as disease-progression value.
Death	0	

The analyses has been conducted according to the economic guidelines already published for Italy (Capri S, Ceci A, Terranova L. et al. Guidelines for economic evaluations in Italy: Recommendations from the Italian Group of Pharmacoeconomic Studies. Drug Information Journal, 2001, 35:189-201;

AIES, Italian Health Economics Association working group. Proposta di linee guida per la valutazione economica degli interventi sanitari in Italia. PharmacoEconomics - Italian Research Articles 2009; 11(2):83-93).

Results

The results presented in Table 8 compare maintenance chemotherapy (both regimen A & B) with adjuvant Mifamurtide treatment to maintenance chemotherapy alone for patients having undergone primary surgery and chemotherapy for treating high-grade non-metastatic osteosarcoma. They are based on the default model assumptions and a 60 year time horizon.

Table 8. Cost-effectiveness of the addition of Mifamurtide (MEPACT)) to Maintenance
Chemotherapy for treating high-grade non-metastatic osteosarcoma

	Undiscounted			Discounted		
Outcome	MEPACT + Maintenance Chemotherapy	Maintenance Chemotherapy Alone	Difference	MEPACT + Maintenance Chemotherapy	Maintenance Chemotherapy Alone	Difference
Total costs	€158,107	€47,138	€110,969	€155,740	€44,919	€110,821
MEPACT Drug costs	€110,963	-	€110,963	€110,963	-	€110,963
Adjuvant Chemotherapy costs	€38,879	€38,879	-	€38,879	€38,879	-
Resource costs	€8,265	€8,259	€6	€5,899	€6,041	-€142
QALYs	37.04	33.58	3.46	18.39	16.88	1.51
Incremental Cost-effectiveness Ratios						
Incremental cost per QALY gained	**€32,111**			**€73,151**		

The undiscounted results show that the Incremental Cost-Effectiveness Ratio (ICER) for Mifamurtide added on maintenance chemotherapy over maintenance chemotherapy alone is € 32,111per Quality Adjusted Life Year (QALY). When discounting is included, the ICER changes to € 73,151 per QALY (Table 8). The primary reason that discounting (of the outcomes) has a significant effect on the ICER is that the majority of the treatment costs are incurred within the first two years of the model but the clinical outcomes are obtained throughout the whole time horizon and thus discounting the outcomes (benefits) reduces the QALY difference between the treatments which adversely affects the cost-effectiveness of Mifamurtide.

Sensitivity Analysis

To ascertain the robustness of the model results we have undertaken a range of sensitivity analysis including one-way sensitivity analysis and probabilistic sensitivity analysis (PSA).

One–way sensitivity analysis
The standard sensitivity analysis was based on the following model settings:

- Costs could vary by 40%, excluding drug costs, which are fixed.

- Mortality rates post recurrence and surgery and second-line chemotherapy at recurrence are assumed to vary within their 95% confidence interval.

- Recurrence rates and quality-of-life utility values varied between their 95% confidence interval derived from assuming each utility values follows a Beta statistical

distribution and the total number of people used to derive the utility values are based on the number of people in the Alessi et al., 2007 study.

- Discounting varied between 0% and 6%.

Figure 2 shows the results of the sensitivity analysis in the form of a tornado diagram. A tornado diagram allows us simultaneously to compare one-way sensitivity analysis for many input parameters and the ICER. The length of the bar represents the sensitivity of the parameter to the ICER. Figure 2 shows that there are in reality only 2 variables that affect the ICER. The most sensitive of these is the discount rate for the outcomes, already discussed.

If the clinical outcomes discount rate is set to its lower rate of 0% (while the discounting rate for costs remains at 3.0%) the ICER becomes €32,268per QALY. Setting the clinical outcomes discount rate to its higher rate of 6% the ICER becomes €134,634 per QALY. The next sensitive parameter is the HRQoL utility value for disease-free health state. If this value is increased from its default value of 0.75 to its higher value of 0.87 then the ICER becomes €71,343 per QALY. Conversely, decreasing this value to its lower value of 0.62 produces an ICER of €103,216 per QALY.

Figure 2: One Way Sensitivity Results
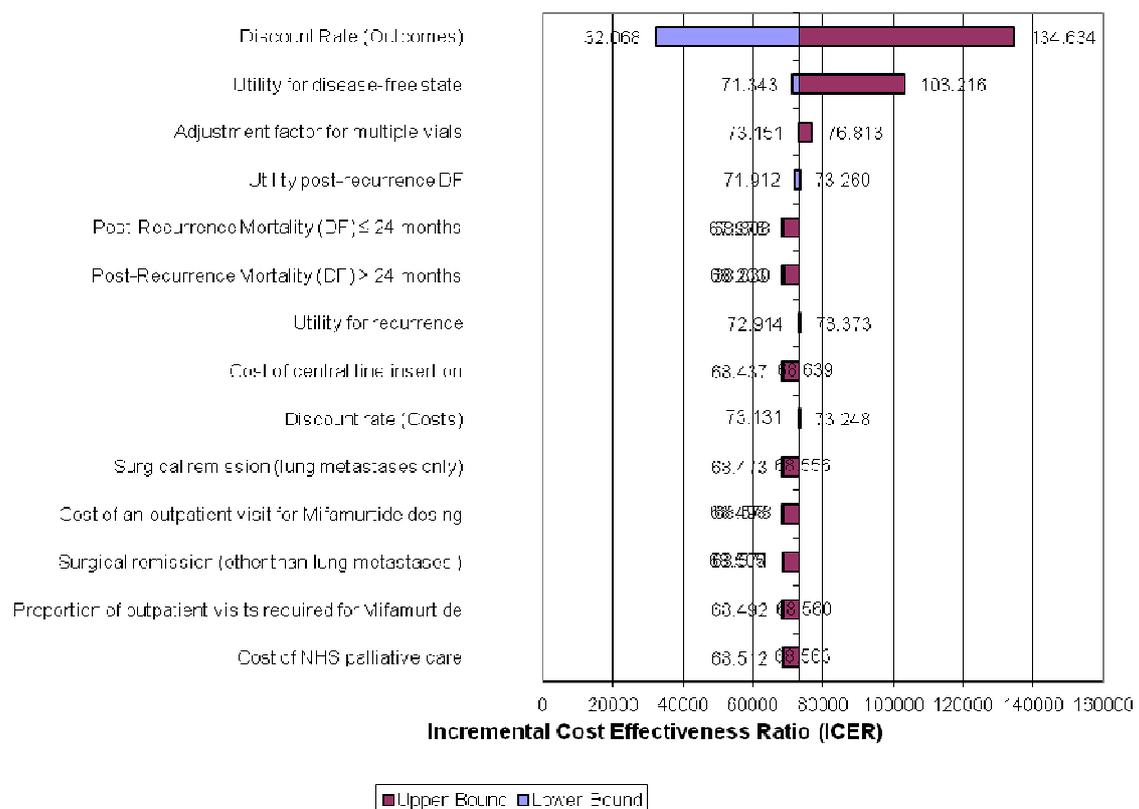
Different results might be obtained by including other model assumptions which can be either included or excluded. In particular they include:

- Incorporating amputation and limb salvage costs;
- Incorporating hearing loss adverse events;
- Allowing the post-recurrence mortality rate to equate to the general population mortality rate for patients who remain disease-free after a given time period.

Table 9 outlines the effect of incorporating these changes. Including the amputation and limb salvage costs changes the ICER from € 32,111 to € 8,625 for the undiscounted results and from € 73,151 to € 79,672 for the discounted result. The inclusion of this variable only affects the cost element of the ICER calculation. The amputation and limb salvage costs are applied to the proportion of patients who, according to the clinical trial data, entered the maintenance phase of treatment having received limb salvage or amputation during the treatment phase. The increase in the ICER is due to the increase in treatment costs being higher for the Mifamurtide arm as more patients survive in the Mifamurtide arm than the standard chemotherapy arm.

Incorporating the hearing loss adverse events assumes that 15% patients receiving Mifamurtide added on chemotherapy and 8% of patients receiving chemotherapy alone have hearing impairment. The hearing loss assumption affects both the costs and QALYs as a utility decrement of 18% is applied to these patients together with extra resource costs. The result is an increase to €39,020 and €91,179 per QALY for the undiscounted and discounted ICER, respectively.

Table 9: Sensitivity Analysis: Inclusion of other Model Assumptions Mifamurtide (MEPACT)

		Discounted		
Parameter	**Outcome**	**MEPACT + Maintenance Chemotherapy**	**Maintenance Chemotherapy Alone**	**Difference**
Default	Total costs	€155,740	€44,919	€110,821
	QALYs	18.39	16.88	1.51
	ICER			**€73,151**
Incorporate Amputation and Limb Salvage costs	Total costs	€270,922	€150,218	€120,701
	QALYs	18.39	16.88	1.51
	ICER			**€79,672**
Incorporate Hearing Loss AE's	Total costs	€155,948	€45,043	€110,905
	QALYs	17.81	16.59	1.22
	ICER			**€91,179**
Post-recurrence mortality rate equal Gen pop rate after 5 years DF	Total costs	€155,640	€44,808	€110,831
	QALYs	19.57	18.18	1.39
	ICER			**€79,713**

		Undiscounted		
Parameter	**Outcome**	**MEPACT + Maintenance Chemotherapy**	**Maintenance Chemotherapy Alone**	**Difference**
Default	Total costs	€158,107	€47,138	€110,969
	QALYs	37.04	33.58	3.46
	ICER			**€32,111**
Incorporate Amputation and Limb Salvage costs	Total costs	€394,539	€261,058	€133,480
	QALYs	37.04	37.04	3.46
	ICER			**€38,625**
Incorporate Hearing Loss AE's	Total costs	€158,455	€47,329	€111,126
	QALYs	35.86	33.01	2.85
	ICER			**€39,020**
Post-recurrence mortality rate equal Gen pop rate after 5 years DF	Total costs	€158,139	€47,175	€110,965
	QALYs	40.25	37.13	3.12
	ICER			**€35,563**

When the mortality risk for post-recurrence disease-free patients returns to that equivalent to the general population after 5 years, ICER increase to €35,563 and €79,713 per QALY for the undiscounted and discounted calculation, respectively. The inclusion of this assumption has the effect of increasing the ICER as it reduces the mortality of patients in the post-recurrence disease-free health states. These health states contain a higher proportion of patients treated in

the standard chemotharpy alone arm than on the Mifamurtide arm, due to the patients on the standard chemotherapy alone arm having a higher recurrence rate. Altering the time point where patients revert to the general population mortality rates effects the ICER also. Increasing the time point at which the mortality rates change lessens the effect on the ICER, while decreasing the time point increases the effect on the ICER.
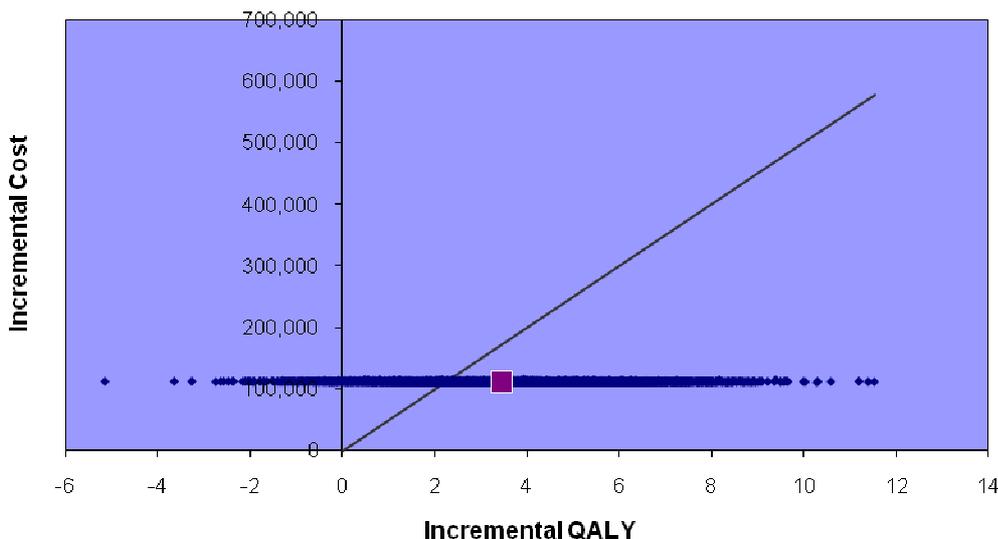
Probabilistic Sensitivity analysis

The PSA was run for 10,000 model iterations using the default scenario with both zero and 3.0% discounting rates for both cost and outcomes. In each probabilistic sensitivity analysis iteration, the model simultaneously sampled parameter values from assumed statistical distributions.

The results of the probabilistic sensitivity analysis are shown in Figure 3 and Figure 4 for the undiscounted results and Figure 5 and Figure 6 for the discounted results. Both analyses have assumed a willingness to pay (WTP) threshold of €50,000. Both analyses also reflect the affect of having the treatment cost primarily in the early years (mainly year 1) by the flatness of the cost-effectiveness scatter plot.

The undiscounted results show that at a WTP threshold of €50,000 around 76.4% of the iterations were below this limit.
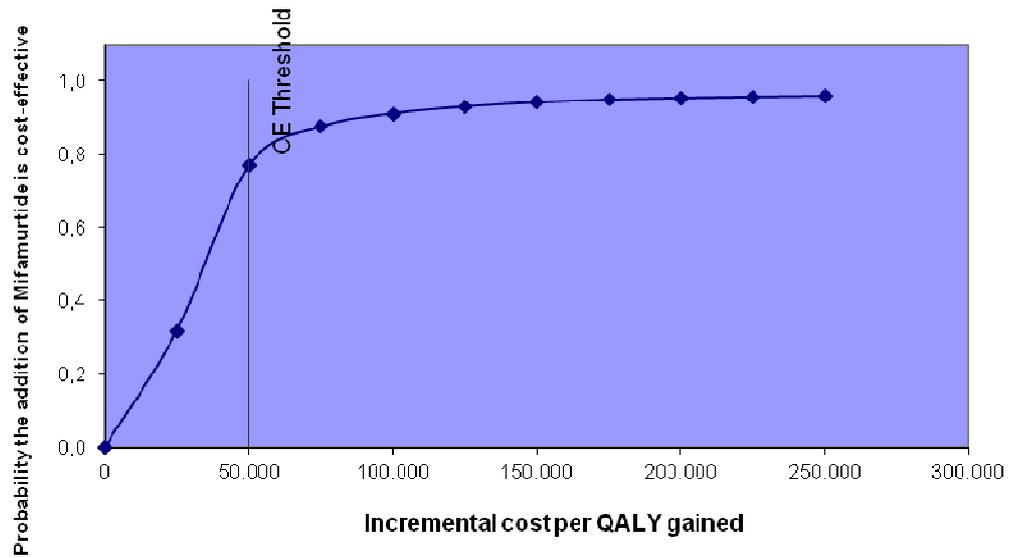
The discounted results show that at a WTP threshold of €50,000 only 19.4% of the iterations were below this limit.

Figure 3: PSA Cost-effectiveness Plot: Undiscounted

PSA = probability sensitivity analysis; QALY = quality-adjusted life-year.

Figure 4: Cost-effectiveness Acceptability Curve: Undiscounted

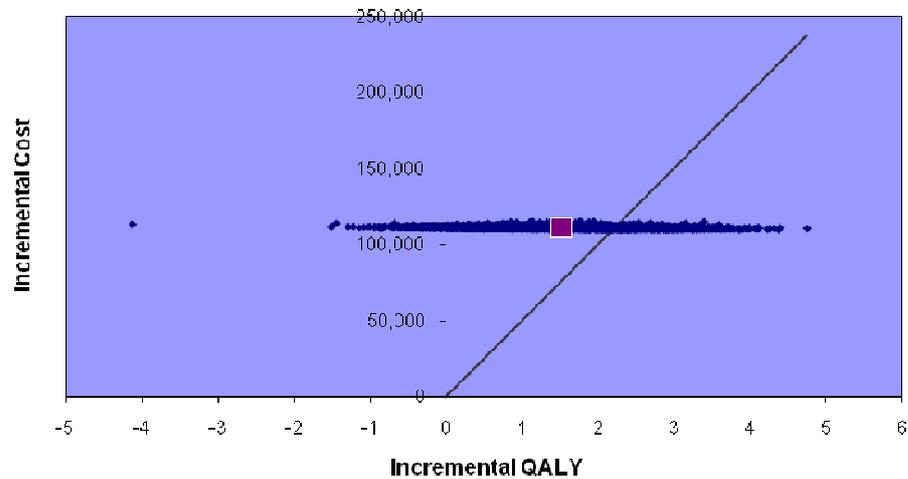CE = cost-effectiveness; QALY = quality-adjusted life-year.

Figure 5: PSA Cost-effectiveness Plot: Discounted

Figure 6: Cost-effectiveness Acceptability Curve: Discounted
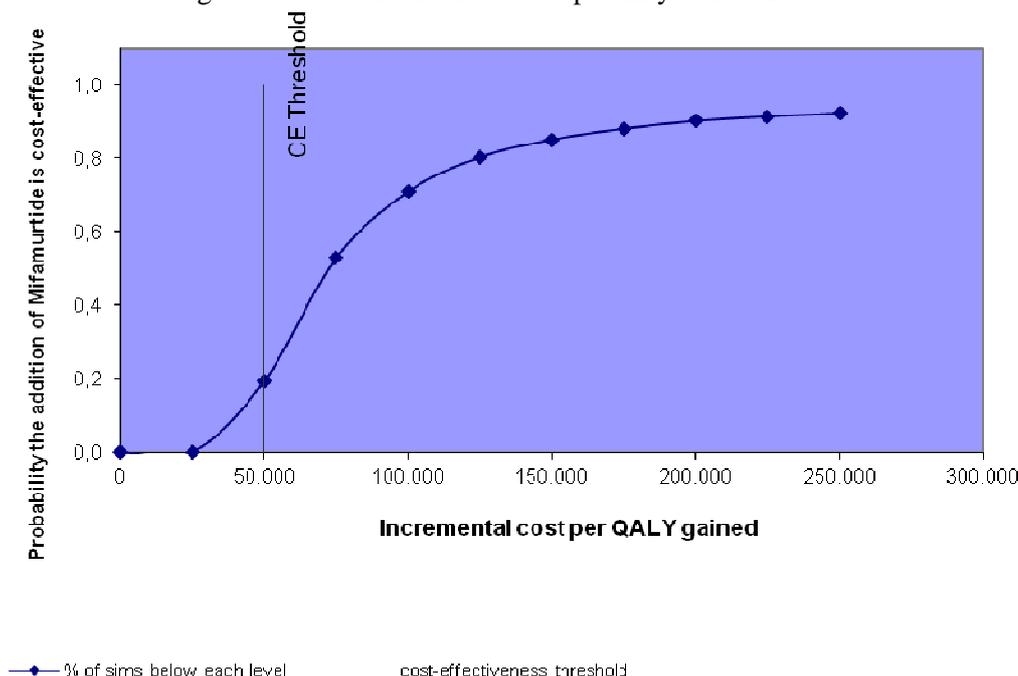
Discussion

There are a number of issues that may limit the robustness of the efficacy data in these clinical trials. It is worth noting actually that clinical trials of cancer treatments used in the adjuvant setting are rarely adequately powered to detect significant differences in overall survival and, when these become apparent, it is usually after lengthy follow-up.

There are some limitations in the economic analysis due to the lack of data and the mechanic of the simulation model. Firstly, as has been observed by Pandor et al. (2009) (Pandor A, FitzGerald P, Stevenson M, Papaioannou D. Mifamurtide for osteosarcoma: A Single Technology Appraisal. ScHARR, The University of Sheffield, 2009) there is no consideration of the variability of efficacy estimates in the economic evaluation (in a further new model it would be possible, with an update of the ongoing clinical trial follow-up of Mifamurtide to attempt to explore the effect of different hazard ratio values on the cost-effectiveness results). Secondly, utility values are not related to the Italian population, but to UK population, given the lack of Italian Studies at the moment with the EQ-5D in this context . However, in Italy it remains still a standard accepted practice for Economic evaluation studies. Thirdly, apart from drug costs, all other resources are estimated using public tariffs, despite the known limits they have compared to the market price, especially in reference to the Tariffs DRGs, where the economic choices of hospitals can be influenced by administrative and reimbursement considerations rather than economic, i.e. of allocative efficiency . In the present analysis, the

tariffs of Lombardy, the largest region in Italy, have been chosen as reference, as the national rates are not updated. Fourthely, although hearing loss is a rare event in these patients, when it occurs might have a strong impact on total costs. When included in the analysis the ICER increases to € 91,179, high value, even still compatible with the benchmark of orphan drug, as it is shown hereafter in the discussion. It is noteworthy that it was no possible to estimate the Italian cost for this adverse event and the UK data has been assumed in the model.

The model described in this study shows that the deterministic ICER for the undiscounted results is € 32,111 per QALY, while applying a discount rate for both costs and outcomes of 3% produces an ICER of € 73,151 per QALY.

This difference in results, due to discounting the outcomes, shows that this is the most sensitive variable on the results. The sensitivity results also showed that the utility value for the disease-free health states of 0.75 is another sensitive parameter.

This large difference between the discounted and non-discounted value is to be referred to the fact that treatment costs are incurred within the first two years, whereas the benefits occur many years later, as the simulation is lifetime (60 years).

However, the value of € 73.151 per QALY gained seems to be relatively low when compared to the ICER of orphan drugs already marketed and reimbursed. Since similar comparison for Italian studies of orphan drugs are not available, it is valuable to take as comparison the values of ICERs of orphan drugs estimated by NICE in UK. As shown in Table 1 (NICE. Appraising Orphan Drugs 16 March 2006) the values of the ICER are mostly much higher than those obtained in the present study , even taking into account possible differences due to the different context of the country.

Since for decision-makers not only the ICER value is important, but also the budget impact of the drug, the most considered today by the central health authorities in Italy (AIFA, the Italian Medicines Agency), it is noteworthy that the impact of Mifamurtide is considerably below the impact that the other orphan drugs have on pharmaceutical expenditure in Italy. First, bear in mind the study already quoted Arcimed (2007), the Independent Study conducted on behalf of the European Commission to evaluate the conditions orphan drugs for marketing in the EU, which has showed the existence of an inverse relationship between the exponential expenditure for the yearly expenditure for patient and the prevalence of the disease, in terms of number of patients treated per year. As can be seen in Figure 7, the number of patients decrease proportionally more quickly than the annual cost of drugs marketed and reimbursed. This situation is similar to that found in Italy.

Figure 7. Relationship between yearly cost of treatment per patient and prevalence for orphan drugs
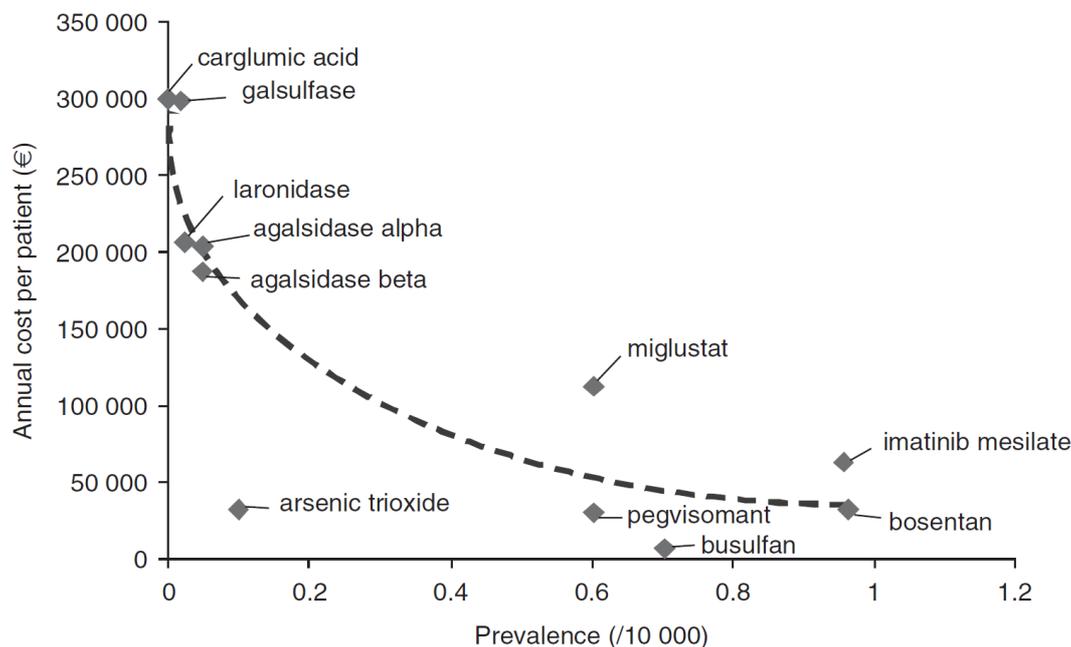
(Adapted from Alcimed, 2005.)

Also AIFA representatives examined the decisions made for orphan drugs approved in Italy over the past years, then they verify the same inverse relationship between the yearly cost per patient and the prevalence (Messori A, Cicchetti A, Patregani L. Relating price determination to disease prevalence. BMJ 2010; 341:c4615). The following equation was developed by fitting the data pairs of [yearly cost per patient] and [patients] for 17 orphan drugs:

$$[\text{yearly cost per patient}] = 2{,}000{,}000 \text{ x e}^{-0.004} \text{ x } [\text{patients}] + 10{,}000$$

The equation is intended to be used only when the disease prevalence is less than 2 cases per 10,000 people.

The exponential curve confirms the result showed by the Alcimed report for the Italian setting. Therefore if we we input in the equation the prevalence of osteosarcoma, the corresponding yearly cost per patient is about € 1,350,640, which is incomparable higher than the real yearly cost of Mifamurtide €138,720. Moreover, by putting the cost of Mifamurtide in the equation, a prevalence of 700 results, which is about seven times higher than the osteosarcoma prevalence in Italy.

Therefore the budget impact of Mifamurtide, even only in terms of pharmaceutical expenditure, has an yearly cost of €138,720, which is substantially low when compared to all orphan drugs already approved in Italy. It is noteworthy that the yearly cost per patient is to be

faced for the whole lifetime of the patient suffering from a rare disease, whereas the treatment of osteosarcoma with Mifurtide lasts just nine months for one shot therapy..

Moreover, if the central health authority (AIFA) would prospect a reduction of the current prices of marketed ultra orphan drugs, in approximately 5 years, by 25% (Policy A) or 50% (Policy B) or 75% (Policy C), as reported in a further paper authored by AIFA representatives (Messori A. Translating the choice to reduce orphan drug prices into quantitative decisions, Letter, BMJ, 4 October 2010). the equation reported above will be rearranged, but still the yearly cost per patient of Mifamurtide would do not require any reduction, since still below the cut offs obtained by the new equation

The present economic evaluation might help the decision makers for an increasing transparency in the resources allocation process.

In many occasion the final decisions are based on decision making process rather than the strict application of cost-effectiveness threshold (Rawlins MD, Culyer AJ. National Institute for Clinical Excellence and its value judgments. BMJ. 2004;329:224-227), and even that, the result of Mifamurtide, also considering the ICER variability showed in the sensitivity analysis, seems to be encouraging as cost-effectiveness analysis of an orphan drug.

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Sommario

Vi sono ancora dei bisogni insoddisfatti che necessitano ulteriore ricerca nei modelli di valutazione economica dei farmaci orfani. Nella prima parte del paper sono stati sviluppati alcuni temi relativi ai limiti della valutazione di costo-efficacia nelle malattie rare. Per approfondire alcuni di questi aspetti teorici in pratica di un nuovo farmaco per l'osteosarcoma. Gli osteosarcomi sono tumori rari: circa 750-900 nuovi casi sono diagnosticati ogni anno negli USA, e di questi 400 colpiscono bambini e adolescenti al di sotto dei 20 anni.

Nella seconda parte del paper è stato valutato il costo-efficacia di mifamurtide, quale trattamento aggiunto alla chemioterapia standard per sarcoma di alto grado non metastatico non resecabile, confrontato con la chemioterapia standard utilizzando un modello di Markov. L'orizzonte temporale era la durata di vita e la prospettiva quella del Servizio Sanitario Nazionale. I risultati non scontati hanno mostrato un ICER per mifamurtide aggiunta alla chemioterapia di mantenimento rispetto alla sola chemioterapia pari a €32.111 per QALY. L'ICER scontato è pari a €73.151. il principale motivo di questa differenza è dovuta al fatto che il trattamento con mifamurtide dura solamente i primi due anni, mentre vantaggi si verificano molto in là nel tempo. L'analisi di sensibilità probabilistica mostra che ad un valore soglia di WTP di €50.000 circa il 76,4% delle simulazioni resta sotto tale valore, ma solamente il 19.45 quando i valori sono scontati. Tuttavia, il valore di €73.151 per QALY guadagnato sembra essere relativamente basso quando confrontato con gli ICER di farmaci orfani già sul mercato e rimborsati in Europa.

Abstract

There is still an unmet need for intensified research into health economic evaluation models of orphan drugs. In the first part of the paper some main issues related to the limits of cost-effectiveness in rare diseases are developed. In order to investigate the theoretical aspect in practice, a cost-effectiveness analysis has been performed to a new drug in osteosarcomas. Osteosarcomas are rare tumors: approximately 750 to 900 new cases are diagnosed each year in the United States, of which 400 arise in children and adolescents younger than 20 years of age.

In the second part of the paper the cost-effectiveness of mifamurtide as add-on treatment to standard chemotherapy for the high grade resectable non metastatic osteosarcoma, compared to standard chemotherapy alone has been evaluated by using a Markov model. The horizon was lifetime and the perspective of the Italian National Health Service has been applied.

The undiscounted results show that the ICER for mifamurtide added on maintenance chemotherapy over maintenance chemotherapy alone is € 32,111per Quality Adjusted Life Year (QALY). When discounting is included, the ICER changes to € 73,151 per QALY. The primary reason that discounting (of the outcomes) has a significant effect on the ICER is that the majority of the treatment costs are incurred within the first two years of the model but the clinical outcomes are obtained throughout the whole time horizon and thus discounting the outcomes (benefits) reduces the QALY difference between the treatments which adversely affects the cost-effectiveness of mifamurtide. The Probabilistic Sensitivity show that at a WTP threshold of €£50,000 around 76.4% of the iterations were below this limit (undiscounted), but only 19.4% when discounted. 19.4% of the iterations were below this limit. However, the value of € 73.151 per QALY gained seems to be relatively low when compared to the ICER of orphan drugs already marketed and reimbursed in Europe.

Nota biografica sugli autori

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Stefano Capri è un economista sanitario, formatosi all'Università Bocconi di Milano e all'Università di York (UK). E' Professore a Contratto di Economia Politica e Economia Industriale presso l'Università Cattaneo-LIUC di Castellanza, e responsabile per le valutazioni economiche presso il Centro HTA dell'Università Cattolica di Roma. Ha ricoperto incarichi di insegnamento in numerose università tra cui la Bocconi, l'Università degli Studi di Milano, l'Università di Firenze, l'Università di Pavia e l'Università Vita-Salute San Raffaele. Ha realizzato valutazioni economiche in numerosi campi della medicina incluso programmi di screening, vaccinazioni, dispositivi medici e farmaci (tra gli altri oncologia, malattie cardiovascolari, diabete, AR, oftalmologia, SNC, disturbi mentali, osteoporosi, AIDS, malattie rare). Ha pubblicato estensivamente sulle maggiori riviste di economia sanitaria. Il suo lavoro riguarda vari temi: valutazione economica delle tecnologie sanitarie, analisi delle politiche e dei sistemi sanitari, economia del farmaco, prezzi e rimborsi dei farmaci, temi teorici relativi all'analisi costo-efficacia.

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