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ORIGINAL ARTICLE

Cost per patient and potential budget implications of denosumab compared with zoledronic acid in adults with bone metastases from solid tumours who are at risk of skeletal-related events: an analysis for Austria, Sweden and Switzerland

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ABSTRACT

Objectives To assess cost implications per patient, per year, and to predict the potential annual budget impact when patients with bone metastases secondary to solid tumours at risk of skeletal-related events (SREs) transition from zoledronic acid (ZA; 4 mg every 3–4 weeks) to denosumab (120 mg every 4 weeks) in Austria, Sweden and Switzerland.

Methods Country specific costs for medication and administration, patient management and SREs (defined as pathologic fracture, radiation to bone, surgery to bone and spinal cord compression) were assessed over a 1-year time horizon. Drug administration and patient management costs were taken from available public sources. SRE costs were based on local unit costs applied to country specific healthcare resources obtained from a multinational retrospective chart review study. Due to lack of real world data for the included countries, SRE rates were derived from phase III clinical trials in patients with advanced cancer and bone metastases. These trials demonstrated that denosumab was superior to ZA in the reduction of SREs.

Results Estimated total annual cost savings for each patient transitioned from ZA to denosumab varied by country and cancer type, ranging from €1583 to €2375 in Austria, from €1980 to €2319 in Sweden (9.1 SEK/€) and from €3408 to €3857 in Switzerland (1.2 CHF/€). Cost savings were mainly driven by the lower SRE related costs and lower administration costs of denosumab compared with ZA.

Conclusions Denosumab offers superior efficacy compared with ZA in patients with solid tumours and bone metastases. Cost savings are predicted in the Austrian, Swedish and Swiss healthcare systems following treatment transition from ZA to denosumab.

INTRODUCTION

Patients with advanced solid tumours commonly develop bone metastases.[1] Bone metastases cause bone destruction through increased osteoclast activity,[1] frequently resulting in skeletal complications known as skeletal-related events (SREs; commonly defined as pathologic fracture, radiation to bone, surgery to bone and spinal cord compression). SREs are associated with significant and debilitating pain, impaired morbidity, reduced quality of life,[2 3] substantial health-resource utilisation[4] and associated costs.[5]

Bisphosphonates are bone targeted agents that have been historically used to reduce the risk of SREs in patients with bone metastases. Zoledronic acid (ZA; Zometa®, Novartis) has been considered the standard of care and has been shown to prolong time to first SRE and reduce the number of SREs; however, many patients with bone metastases continue to experience SREs. ZA is infused intravenously (IV) every 3–4 weeks and is associated with renal toxicity (necessitating monitoring of renal function prior to each infusion).[6] Clinic visits for administration are, on average, 100 minutes in duration.[7]

Denosumab (Xgeva®, Amgen Inc.) has a different and novel mode of action; it is the first fully human monoclonal IgG2 antibody that binds to RANK ligand. RANK ligand is an essential mediator of the formation, activation and survival of osteoclasts.[1] Denosumab (120 mg subcutaneous injection (SC) every 4 weeks) was compared with ZA (4 mg IV every 4 weeks) in three identically designed phase III head to head clinical trials of patients with bone metastases from solid tumours (breast cancer, prostate cancer and other solid tumours or multiple myeloma (ClinicalTrials.gov: NCT00321464, NCT00321620 and NCT0033075)). In patients with solid tumours, denosumab was superior to ZA in reducing the risk of first on-study SREs and delaying the time to multiple (first and subsequent) SREs compared with ZA. Patients treated with denosumab also experienced fewer SREs overall than those treated with ZA.[8–10] Denosumab does not require renal monitoring. The overall incidence of adverse events was similar between denosumab and ZA.[8–10]

The objective of the analyses reported in this paper was to assess the cost implications per patient, per year, and to predict the potential annual budget impact when patients with bone metastases secondary to solid tumours at risk of SREs transitioned from treatment with ZA (4 mg IV every 3–4 weeks) to treatment with denosumab (120 mg SC, every 4 weeks) in Austria, Sweden and Switzerland.

METHODS

Design

Analyses included country specific cost implications for medication, administration, patient management and SRE related costs per patient, per year,

the resulting cost difference per patient, per year, and the prediction of potential annual budget impact with treatment transition from ZA to denosumab in patients with bone metastases from solid tumours. Real world data on the frequency of administration of ZA were used in the main analyses. The analyses included the following cost components: medication and administration, patient management and SRE related costs.

Resource use and costs

Drug unit costs

Drug unit costs were based on the available 2012 public prices in each of the countries (table 1); medication cost analyses were based on the drug unit costs and the frequency of administration of ZA and denosumab. The summary of product characteristics for ZA recommends administration every 3–4 weeks,[6] and evidence suggests that there is equivalent efficacy between these two administration schedules.[11] For the purposes of these analyses, information on the frequency of ZA administration every 3 weeks in routine medical practice were obtained from a market research audit, the European Tandem Oncology Monitor (ETOM).[12] The number of ZA administrations per year, per tumour type, were estimated based on the average number of patients receiving ZA every 3 weeks in Germany, Italy, Spain, the UK and France, due to the lack of such data for Austria, Sweden and Switzerland. The percentage of patients receiving ZA every 3 weeks was estimated to be 20.7% in breast cancer, 36.4% in prostate cancer and 29.1% in other solid tumours. This corresponds to 13.9, 14.6 and 14.3 doses per year of ZA in breast cancer, prostate cancer and other solid tumours, respectively. For denosumab, the approved administration schedule is once every 4 weeks, corresponding to 13 doses per year.[13] In the base case analysis, the presented real world administration frequencies were used for ZA. Sensitivity analyses are presented for the scenario where both ZA and denosumab are administered every 4 weeks.

Administration and patient management costs

For Austria, unit costs were based on physicians' fee scales across provinces,[14] outpatient tariffs set in one province for self-paying patients (as a proxy for outpatient costs),[15] and national diagnosis and procedure related reimbursement rates for inpatients.[16]

For Sweden, base case drug administration costs were estimated from the mean of two hospital price lists that were judged to be representative of costs across the entire country.[17 18]

For Switzerland, drug administration costs were based on publicly available tariff costs. Additional cost information was gathered using a doctors' survey to identify the TARMED[19] items (outpatient tariff codes used in Switzerland) charged for IV and SC administration.

Patient management costs, including creatinine tests, were derived from publicly available sources in each of the countries.[14 20–22]

SRE rates and costs

In the absence of available real world SRE rates for the countries included in these analyses, annualised SRE rates for ZA were estimated for each tumour type, using the total number of SREs observed and total person years of follow-up in the above mentioned denosumab phase III clinical trials (table 2).[8–10] Rates for denosumab were estimated by applying the rate ratios representing treatment effects (ie, times to first and subsequent SREs) of denosumab compared with ZA on the baseline ZA SRE rate.

The costs per SRE type for each country were generated by applying local unit costs applied to country specific SRE related healthcare resource use obtained from a multinational retrospective chart review study (20090146 study).[5] This study enrolled patients with bone metastases or bone lesions secondary to breast cancer, prostate cancer, lung cancer or multiple myeloma from centres in Austria, the Czech Republic, Finland, Greece, Poland, Portugal, Sweden and Switzerland. Health-resource utilisation extracted from patient charts included inpatient stays, outpatient visits, day care visits, emergency room visits and procedures. Cost of SREs by SRE type for Austria and Sweden were derived from this study and have been reported previously, as listed in table 1.[5] For Switzerland, SRE costs were calculated slightly differently as a sum of inpatient visits, outpatient visits and outpatient procedure costs (table 1).[23 24] In order to estimate outpatient visit costs, additional information was obtained from a physicians' survey among physicians aimed at identifying the typical outpatient tariff (TARMED[19]) codes charged for outpatient consultations. Average costs were estimated based on Swiss Cantonal costs per TARMED point.[19 25] Mean number of inpatient stays and health-resource utilisation estimates for the number and duration of inpatient visits were taken from the 20090146 study. A weighted average of adjusted length of stay was calculated based on hospitalisation statistics of the Organisation for Economic Cooperation and Development. Data

Table 1 Local unit costs by country

	Austria	Sweden	Switzerland
Drug and administration costs (per administration) (€)			
Price denosumab 120 mg*	371.00	354.40	452.46
Price zoledronic acid 4 mg*	303.10	308.79	336.71
Administration cost—denosumab (SC)	10.98	46.48	47.94
Administration cost—zoledronic acid (IV)	29.55	151.10	144.79
Patient management costs (per test) (€)			
Laboratory test (serum creatinine test)	7.46	3.08	2.10
SRE costs (per SRE event) (€)			
Pathologic fracture	10 305	5 802	25 987
Radiation to bone	14 603	3 305	13 407
Surgery to bone	21 496	10 783	49 330
Spinal cord compression	22 191	13 143	51 188

*Per 4 week cycle
SRE, skeletal-related event.

Table 2 Skeletal-related event rate and distribution by type

	Breast cancer	Prostate cancer	Other solid tumours
SRE rate (per year)			
Zoledronic acid	0.631	0.947	0.936
Denosumab (derived)	0.486	0.777	0.796
Denosumab treatment effect			
Rate ratio first and subsequent SRE	0.77	0.82	0.85
SRE type distribution* (%)			
Pathologic fracture	58.2	26.8	31.4
Radiation to bone	35.4	66.1	57.5
Surgery to bone	4.7	1.5	6.2
Spinal cord compression	1.7	5.6	5.0

*Pooled across both treatment groups.
SRE, skeletal-related event.

from the Swiss National Statistics Office were used to calculate the cost of hospital stays.[26]

Costs are reported in Euros (€). Swedish and Swiss costs were converted to Euros using exchange rates of 9.1 SEK/€ and 1.20 CHF/€, respectively.

RESULTS

Estimates of cost implications per patient, per year, included the costs of drugs and drug associated patient management (creatinine test) costs, administration and SRE costs, as shown in table 3.

In all countries, treatment transition from ZA to denosumab (using real world data on the frequency of administration of ZA) was predicted to generate cost savings (table 3). The estimated total annual cost savings per patient transitioned from treatment with ZA to denosumab varied by country and tumour type and ranged from €1583 to €2375 in Austria, from €1980 to €2319 in Sweden and from €3408 to €3857 in Switzerland. The cost savings were mainly driven by the delay in the time to the first and first and subsequent SREs, the lower SRE related costs and administration costs of denosumab compared with ZA. Given the higher SRE related costs estimated for Austria and Switzerland compared with Sweden, reductions in SRE related costs had a greater impact in Austria and Switzerland. The administration cost savings were significantly higher in Sweden and Switzerland compared with Austria, due to the unit cost difference associated with IV and SC administration.

The total annual budget implications per country for patients that transition treatment from ZA to denosumab depends on the actual transition rate across the different tumour types. Figure 1 illustrates the cost saving predictions following treatment transition from ZA to denosumab for up to 1500 patients for each tumour type in Austria, Sweden and Switzerland. Based on these findings the predicted total annual cost savings for every 1000 patients transitioned from ZA to denosumab ranged from €1.6 to €2.4 million in Austria, from €2.0 to €2.3 million in Sweden and from €3.4 to €3.6 million in Switzerland.

Sensitivity analyses were conducted for cost related inputs (administration and SRE related costs), trial based data on the frequency of administration of ZA (every 4 weeks) and baseline ZA risk (ZA SRE rate). Administration and SRE related costs varied by ±50%. The baseline ZA SRE rate for patients receiving ZA varied by +100% and −50% based on the results of a recent US study indicating that the real world SRE rate may be substantially higher (up to twofold) than the trial based rates used in the current analyses.[27] These sensitivity analyses confirmed the robustness of the results (see online supplementary appendix tables A1–3).

In addition to the above sensitivity analyses, price threshold analyses were conducted to assess the impact of expected price reductions for ZA following generic formulation entry due to loss of patent protection in the middle of 2013. The threshold analyses present the maximum price reduction for ZA that will still maintain the overall cost saving results of denosumab given the currently available prices for ZA (see online supplementary appendix table A4). If the prices for ZA in comparison with the current prices as presented in table 1 are reduced by more than the threshold value, denosumab may no longer be cost saving. The results from the ZA price threshold analyses reveal a very strong cost savings impact of denosumab, even with significant price reductions for ZA in all three countries. Denosumab remains cost saving even with price reductions for ZA of up to 38–54% in Austria, 46–52% in Sweden and 71–79% in Switzerland.

If the ZA price reduction is greater than the threshold value, treatment transition to denosumab will increase costs associated with treatment. In this situation, a cost effectiveness analysis would be in order, where the incremental costs for denosumab could be contrasted against the improved patient health related quality of life obtained as a consequence of the clinical

Table 3 Cost implications per patient per year by cost category, tumour type and country

	Breast cancer		Prostate cancer		Other solid tumours	
	Denosumab	Zoledronic acid*	Denosumab	Zoledronic acid*	Denosumab	Zoledronic acid*
Austria						
Cost of drugs	4823	4212	4823	4418	4823	4323
Cost of administration/management	143	514	143	540	143	528
Cost of SREs	6100	7922	10856	13239	11198	13174
Total costs	11066	12648	15821	18196	16164	18024
Total cost difference (denosumab vs ZA)	−1583 (12.5%)		−2375 (13.1%)		−1861(10.3%)	
Sweden						
Cost of drugs	4607	4291	4607	4501	4607	4404
Cost of administration/management	604	2143	604	2248	604	2199
Cost of SREs	2564	3330	3601	4392	4016	4725
Total costs	7775	9764	8812	11140	9228	11327
Total cost difference (denosumab vs ZA)	−1988 (20.4%)		−2328 (20.9%)		−2100 (18.5%)	
Switzerland						
Cost of drugs	5882	4679	5882	4908	5882	4802
Cost of administration/management	623	2041	623	2141	623	2095
Cost of SREs	11204	14550	15091	18403	17095	20112
Total costs	17709	21271	21596	25453	23600	27008
Total cost difference (denosumab vs ZA)	−3562 (16.7%)		−3857 (15.2%)		−3408 (12.6%)	

*Real world data on the frequency of administration of zoledronic acid were used.
All costs are in Euros.
SRE, skeletal-related event; vs, versus; ZA, zoledronic acid.

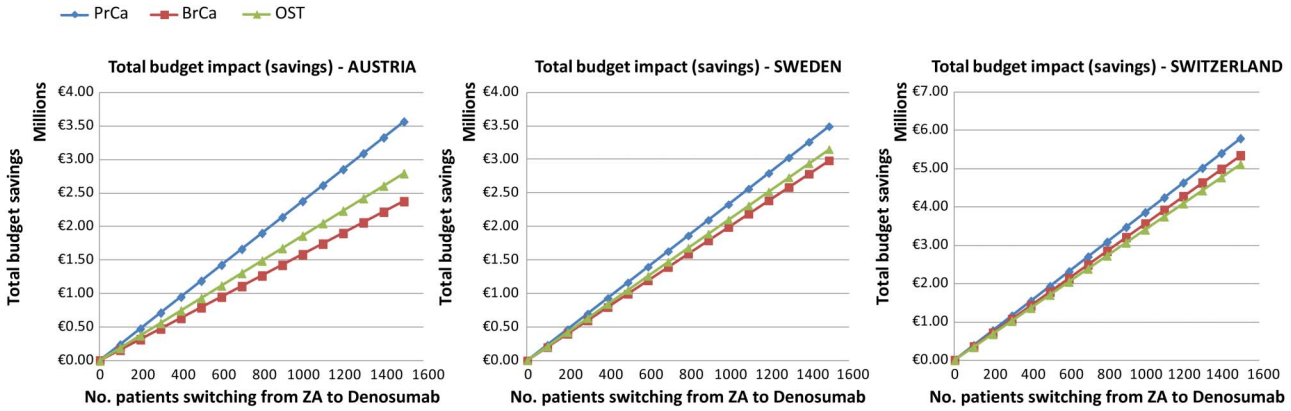

Figure 1 Predicted total budget implications following treatment transition from zoledronic acid (ZA) to denosumab per country and tumour type. BrCa, breast cancer; OST, other solid tumours; PrCa, prostate cancer.

superiority of denosumab. Ultimately, the decision makers' willingness to pay for improvements in health and treatment outcomes will determine this cost effectiveness assessment. A complete cost effectiveness assessment was beyond the scope of this analysis, and the threshold analyses indicated that denosumab will remain cost saving even when accounting for significant price reductions in ZA.

DISCUSSION

Budget impact analysis is a tool for payers at national and regional levels and contributes to informed decision making on the most efficient allocation of healthcare resources. Decisions on the usage of innovative drugs can have a significant impact on patients' health and outcomes. The purpose of this study was to assess the cost implications per patient, per year, the resulting cost difference per patient, per year, and to predict the potential annual total budget impact implications of treatment transition from ZA to denosumab in adults with bone metastases from solid tumours at risk of SREs in the Austrian, Swedish and Swiss healthcare settings.

Across the three countries, treatment transition from ZA to denosumab resulted in substantial cost savings per patient, per year. Denosumab was associated with lower overall SRE related costs due to its clinical superiority over ZA. Additionally, the administration costs of denosumab (administered SC) were lower than those for ZA (infused IV). Sensitivity analyses confirmed the robustness of the results.

One of the main limitations of these analyses was the use of trial based SRE rates due to a lack of real world SRE data in Austria, Sweden and Switzerland. According to the results of a recent study in the USA, the real world SRE rate may be substantially higher (up to twofold) than the trial based rates used in these analyses.[27] Hence these analyses might have underestimated the annualised SRE rates and the value of denosumab. Additionally, some economic benefits to the wider society (eg, a reduction in indirect costs associated with SREs and treatment administration) and the impact on caregivers were not included in this analysis.

Another potential limitation is that the real world data used for the actual frequency of administration of ZA (every 3 weeks vs every 4 weeks) were not based on country specific data for Austria, Sweden and Switzerland as these were not available. Instead, the average frequency of ZA use every 3 weeks that was used in these analyses was estimated from market research data (ETOM) for Germany, Italy, Spain, the UK and France. Furthermore, the analyses were performed using a 1 year time horizon and therefore do not represent the total benefits in terms of cost per patient benefit of denosumab, given that most patients live longer than 1 year.

Finally, as the analyses focused solely on the potential budget implications with treatment transition from ZA to denosumab they did not incorporate the additional clinical benefits observed in the relevant clinical trials associated with denosumab, in terms of improved patient reported outcomes, including health related quality of life and superior delay in pain progression.[28]

CONCLUSION

Denosumab is predicted to offer a cost saving treatment option compared with ZA, with improved clinical outcomes in terms of reduced risk of SREs. Therefore, it represents good value for money in preventing the risk of SREs in patients with bone metastases from solid tumours in Austria, Sweden and Switzerland.

Key messages

- Denosumab offers superior efficacy compared with zoledronic acid in patients with solid tumours and bone metastases.
- Cost savings are predicted in the Austrian, Swedish and Swiss healthcare systems following treatment transition from zoledronic acid to denosumab.

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Contributors ML, AB and PV contributed to the design of this modelling study, the analysis plan, analysed the data, and drafted, revised and approved the final publication. ML is guarantor for these data. ER, LS and WH provided data, application of the model and interpretation from an Austrian perspective, as well as drafting, revising and approving the final publication. JL provided data, application of the model and interpretation from a Swedish perspective, as well as drafting, revising and approving the final publication. AMP and IB provided data, application of the model and interpretation from a Swiss perspective, as well as drafting, revising and approving the final publication.

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Competing interests ML, ER, JL, IB, PV and AB are employees of Amgen. LS and WH are employees of Joanneum Research Forschungsgesellschaft mbH, which received funding from Amgen to conduct this research. AMP has received research funding for the University of Basel from Amgen.

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Table A1: Sensitivity analyses – Breast cancer

Sensitivity analyses – Breast Cancer		Q4W ZA frequency*		Administration costs				SRE costs***				ZA SRE baseline risk			
				-50%		+ 50%		- 50%		+50%		-50%		+100%	
		Dmab**	ZA	Dmab	ZA	Dmab	ZA	Dmab	ZA	Dmab	ZA	Dmab	ZA	Dmab	ZA
Austria	Cost per patient per year	€11066	€12343	€10994	€12443	€11137	€12854	€8016	€8687	€14116	€16609	€8016	€8687	€17165	€20570
	Cost savings per patient per year	-€1278		-€1449		-€1717		-€672		-€2494		-€672		-€3405	
Sweden	Cost per patient per year	€7775	€9348	€7473	€8714	€8077	€10814	€6493	€8099	€9057	€11429	€6493	€8099	€10339	€13093
	Cost savings per patient per year	-€1573		-€1241		-€2736		-€1605		-€2371		-€1605		-€2754	
Switzerland	Cost per patient per year	€17709	€20837	€17397	€20265	€18021	€22277	€12107	€13996	€23311	€28546	€12107	€13996	€28913	€35821
	Cost savings per patient per year	-€3128		-€2868		-€4256		-€1889		-€5235		-€1889		-€6909	

***Q4W = every 4 weeks, ZA = Zoledronic acid, ** Dmab = denosumab, *** SRE=skeletal-related events**

Table A2: Sensitivity analyses – Prostate Cancer

Sensitivity analyses – Prostate Cancer		Q4W ZA frequency*		Administration costs				SRE costs***				ZA SRE baseline risk			
				-50%		+ 50%		- 50%		+50%		-50%		+100%	
		Dmab**	ZA	Dmab	ZA	Dmab	ZA	Dmab	ZA	Dmab	ZA	Dmab	ZA	Dmab	ZA
Austria	Cost per patient per year	€15821	€17660	€15750	€17981	€15893	€18412	€10394	€11577	€21249	€24816	€10394	€11577	€26677	€31435
	Cost savings per patient per year	-€1839		-€2231		-€2519		-€1184		-€3567		-€1184		-€4758	
Sweden	Cost per patient per year	€8812	€10410	€8510	€10039	€9115	€12242	€7012	€8945	€10613	€13336	€7012	€8945	€12414	€15532
	Cost savings per patient per year	-€1598		-€1529		-€3127		-€1933		-€2723		-€1933		-€3118	
Switzerland	Cost per patient per year	€21596	€24690	€21284	€24397	€21907	€26508	€14050	€16251	€29141	€34654	€14050	€16251	€36686	€43856
	Cost savings per patient per year	-€3094		-€3113		-€4601		-€2201		-€5513		-€2201		-€7170	

Table A3: Sensitivity analyses – Other solid tumours

Sensitivity analyses – Other Solid Tumours		Q4W ZA frequency		Administration costs				SRE costs				ZA SRE baseline risk			
				-50%		+ 50%		- 50%		+50%		-50%		+100%	
		Dmab	ZA	Dmab	ZA	Dmab	ZA	Dmab	ZA	Dmab	ZA	Dmab	ZA	Dmab	ZA
Austria	Cost per patient per year	€16164	€17595	€16092	€17814	€16235	€18235	€10565	€11437	€21763	€24611	€10565	€11437	€27362	€31198
	Cost savings per patient per year	-€1432		-€1721		-€2000		-€873		-€2849		-€873		-€3837	
Sweden	Cost per patient per year	€9228	€10743	€8925	€10250	€9530	€12405	€7219	€8965	€11236	€13690	€7219	€8965	€13244	€16052
	Cost savings per patient per year	-€1516		-€1324		-€2875		-€1745		-€2454		-€1745		-€2808	
Switzerland	Cost per patient per year	€23600	€26398	€23288	€25976	€23912	€28041	€15053	€16952	€32148	€37064	€15053	€16925	€40695	€47120
	Cost savings per patient per year	-€2798		-€2687		-€4129		-€1900		-€4917		-€1900		-€6425	

Table A4: Zoledronic Acid price threshold analyses*.

	Breast Cancer	Prostate Cancer	Other Solid Tumours
Austria	37.6%	53.8%	43.0%
Sweden	46.3%	51.7%	47.7%
Switzerland	76.1%	78.6%	71.0%

*Maximum price reduction for ZA at which denosumab still offers overall cost savings.