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Treatment of pulmonary arterial hypertension in Poland – current practice

Survey results

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M. Jakubczyk	– no conflict of interest	B. Osińska	– no conflict of interest

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CONTENTS

KEYWORDS

pulmonary arterial hypertension, survey, epoprostenol, iloprost, treprostinil, bosentan, sildenafil

1 AIM OF THE REPORT

This report presents the results of a survey performed in 6 institutions providing treatment to patients with pulmonary arterial hypertension.

The aim of this survey was to evaluate prevalence and current practice of treatment of patients with NYHA III/IV pulmonary arterial hypertension in Poland as well as expected changes due to introduction of novel drugs: bosentan (Tracleer), epoprostenol (Flolan), iloprost (Ventavis), sildenafil (Revatio) and treprostinil (Remodulin).

Results of this survey were used in the analysis of budget impact of introduction of these drugs in Poland.

2 METHODS OF THE ANALYSIS

2.1 Surveyed institutions

The questionnaire was sent to all identified institutions (6 clinical centres, including one paediatric centre) providing specialist care for patients with pulmonary arterial hypertension in Poland.

2.2 Questionnaire form

The questionnaire has been designed with participation of a clinician (M. Kurzyna, MD, PhD; Institute of Tuberculosis and Lung Diseases, Warszawa), specialist in treatment of pulmonary arterial hypertension. The questionnaire was first piloted in the coordinating centre and then adjusted and used in all other centres.

The questionnaire was designed so as to evaluate prevalence and current practice of treatment of patients with NYHA III/IV pulmonary arterial hypertension in Poland as well as expected changes due to introduction of novel drugs: bosentan (Tracleer), epoprostenol (Flolan), iloprost (Ventavis), sildenafil (Revatio) and treprostinil (Remodulin). The survey consisted of three parts, i.e. epidemiology, current practice, clinical practice following unrestricted drugs availability and corresponding resource use.

The illness dynamics (represented by NYHA class changes) make it difficult for clinicians to assess the average annual resource usage. Thus it was decided to collect data on average annual resource usage regardless of NYHA classification, except for ad hoc (on short-term basis) pharmacological treatment. The questionnaire form is presented below:

We should be most grateful for information concerning clinical management of patients with pulmonary arterial hypertension (PAH) at your institution. The data will be accumulated and processed in order to prepare a budget impact analysis commissioned by the Agency for Health Technology Assessment in Poland; we hope that this analysis will result in significant improvement of availability of novel drugs used in treatment of this severe illness. We would appreciate your answers to the following questions as well as any remarks or comments.

1. How many patients with pulmonary arterial hypertension remain under care of your institution **at present?**
   1.1. Idiopathic PAH ……patients
   1.2. Congenital systemic-to-pulmonary shunts ……patients
   1.3. Connective tissue diseases ……patients
   1.4. Porto-pulmonary hypertension ……patients
   1.5. HIV infection ……patients
   1.6. TOTAL (excluding thromboembolic hypertension, venous pulmonary hypertension and interstitial or obstructive pulmonary diseases (so-called hypoxemic pulmonary hypertension))
   ……patients

2. What percentages of patients with PAH were classified in particular functional classes according to the NYHA/WHO at the time of diagnosis:
   2.1. I ……% of patients
   2.2. II ……% of patients
   2.3. III ……% of patients
   2.4. IV ……% of patients
   2.5. If accurate information concerning distribution of patients among specific classes is difficult to obtain, please specify at least approximate total percentage of patients in class III/IV:
   ……% of patients

3. How many times **in one year** is (does) an average patient with PAH:

   3.1. consulted in outpatient settings (please specify type of the consultation and specialty of the clinic providing this service):
   3.1.1. Type I consultation – …… times a year; specialty:
   …….
   3.1.2. Type II consultation – …… times a year; specialty:
   …….
   3.1.3. Type III consultation – …… times a year; specialty:
   …….

   3.2. require hospitalisation due to clinical worsening (exacerbation of the disease): …… times a year

   3.3. require control hospitalisation not related to clinical worsening: …… times a year

4. What percentage of patients requires long-term home oxygen therapy?
   ……% of patients
5. Pharmacological treatment used in NYHA/WHO class III/IV pulmonary arterial hypertension:

Therapeutic group	Drug/Formulation	Mean **daily** dose	Percentage of patients receiving this drug

Diuretics	1.		
	2.		
	3.		
	4.		
	5.		
Heparins	1.		
	2.		
	3.		
Oral anticoagulants	1.		
	2.		
	3.		
Digoxin	1.		
	2.		
	3.		
Calcium channel blockers	1.		
	2.		
	3.		
	4.		
	5.		
Bosentan			
Epoprostenol			
Iloprost			
Sildenafil			
Treprostinil			
Other – what?	1.		
	2.		
	3.		
	4.		
	5.		

6. Please specify the percentage of patients, in whom combination therapy with two or more of the following drugs is used: bosentan, epoprostenol, iloprost, sildenafil or treprostinil:
…….% of patients

7. Please specify the most commonly used combination therapies (including only drugs listed in Question 6, i.e. bosentan, epoprostenol, iloprost, sildenafil and treprostinil):

7.1.…… + ……..- ……% of patients
(first drug) (second drug)
7.2.…… + ……..- ……% of patients
(first drug) (second drug)
7.3.…… + ……..- ……% of patients
(first drug) (second drug)
7.4.…… + ……..+ ……..- ……% of patients
(first drug) (second drug) (third drug)
7.5.…… + ……..+ ……..- ……% of patients
(first drug) (second drug) (third drug)
7.6.…… + ……..+ ……..- ……% of patients
(first drug) (second drug) (third drug)

8. Taking into consideration indications, contraindications, adverse effects and tolerance, and assuming unlimited availability of the analysed drugs, how often the **first-line drug** will be:

Drug	% of patients
Bosentan	
Epoprostenol	
Iloprost	
Sildenafil	
Treprostinil	

9. Assuming unlimited availability of the analysed drugs, what – in your opinion – will be the target (i.e. stable in the whole group of patients, regardless of time from diagnosis) structure of use of these drugs (i.e. how often will each drug be used in the whole population):

Drug	% of patients
Bosentan	
Epoprostenol	
Iloprost	
Sildenafil	
Treprostinil	

10. Please describe the adverse effects of the analysed drugs most commonly encountered at your institution and their actual management at your institution:

Drug	Adverse effect	Frequency – % of patients	Management of this adverse effect
Bosentan	1.		
	2.		
	3.		
Epoprostenol	1.		

	2.		
	3.		
Iloprost	1.		
	2.		
	3.		
Sildenafil	1.		
	2.		
	3.		
Treprostinil	1.		
	2.		
	3.		

11. Please specify mean number of patients undergoing (or awaiting) the following procedures (annually):
    11.1. Atrial septostomy: ……. patients undergoing this intervention
    11.2. Atrial septostomy: ……. patients awaiting this intervention
    11.3. Pulmonary transplantation: the number of transplantations performed in the last year ……
    11.4. Pulmonary transplantation: the number of patients qualified for transplantation in the last year ……
    11.5. Pulmonary transplantation: the number of patients awaiting intervention ……

12. How many post-transplant patients remain under care of your institution at present: ……..patients

Remarks and comments:

……

……

……

……

……

2.3 Conduction of the survey

The survey was conducted from July 25th till August 31st, 2007. Sample questionnaires and covering letters were posted and sent by e-mail. All doubts regarding filling out of the questionnaires were clarified by phone.

3 RESULTS

All the centres provided complete responses to the questionnaire. Whenever the data needed verification the personal contact has been made.

3.1 Basic clinical data

In total, there were 308 patients (including 19 children) with pulmonary arterial hypertension remaining under care of six highly specialist centres. The most common types of PAH were: idiopathic PAH (133 patients) and PAH associated with congenital systemic-to-pulmonary shunts (147 patients). Prevalence of specific types of PAH is presented in Table 1 and Figure 1. More than a half of the whole population of patients (61.04%) was classified in NYHA class III or IV.

Figure 1.
Prevalence of specific types of PAH in the population of Polish patients

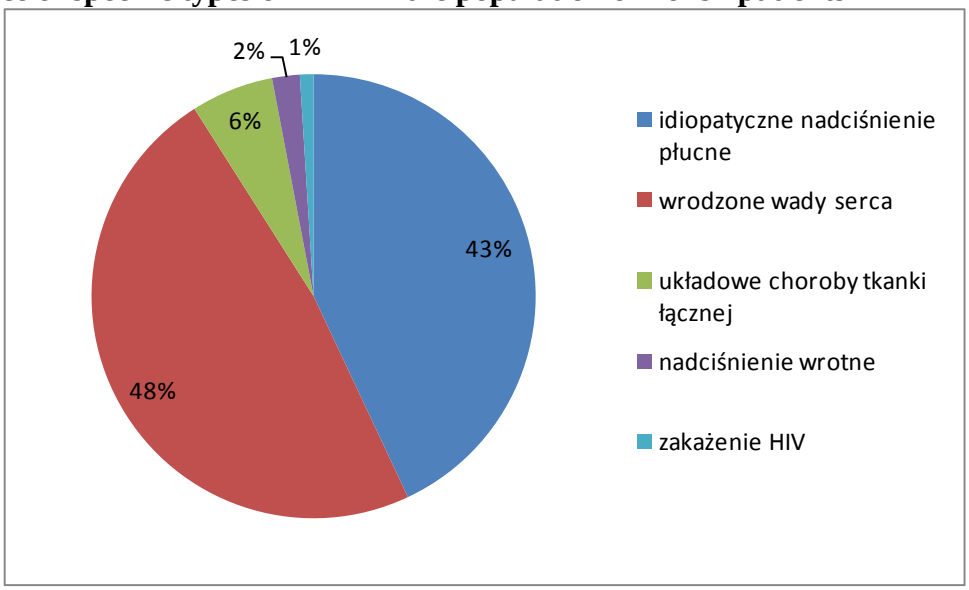


Table 1.
Summary of the survey results – clinical characteristics of the treated population.

	Centre 1	Centre 2	Centre 3	Centre 4	Centre 5	Centre 6
Number of patients with PAH remaining under care of the centre at present	114	19	63	14	81	17
Including:						
Idiopathic PAH	72	8	22	10	11	10
PAH associated with congenital systemic-to-pulmonary shunts	22	11	40	3	68	3
PAH associated with connective tissue diseases	14	0	1	1	1	2
PAH associated with portal hypertension	4	0	0	0	0	1
PAH associated with HIV infection	2	0	0	0	1	1
Number of patients in NYHA class III/IV	63*	6*	50*	11*	50*	8*
* calculated from the specified percentage of patients in NYHA class III/IV, rounded to an integer number						

3.2 Use of medical resources

Results of the survey concerning frequency of hospitalisations (in order to perform control tests or due to clinical worsening) and outpatient consultations in patients with PAH are presented below. Only at two centres the patients remained under care of pulmonology clinics (centre 1 and 6); at the remaining institutions outpatient care for patients with PAH was provided by cardiology clinics. Exact numbers and types of consultations are presented in Table 2.

Average annual number of hospitalisations due to exacerbation of the disease declared by the surveyed centres was 1 to 3.

Declared annual number of hospitalisations in order to perform control tests and periodic assessment of the patient's condition ranged from 0 (at the centre providing care for children with PAH) to 3 (centre 5).

On average, 34.98% of patients required home oxygen therapy; the survey indicated significant differences between particular institutions (from 0 to 80% of patients) in this respect.

Table 2.
Summary of the survey results – medical procedures used annually per patient.

	Centre 1	Centre 2	Centre 3	Centre 4	Centre 5	Centre 6
Type I pulmonary consultation	0	0	0	0	0	1
Type II pulmonary consultation	0	0	0	0	0	2
Type III pulmonary consultation	3	0	0	0	0	2
Type I cardiology consultation	0	0	1	0	0	0
Type II cardiology consultation	0	3	6	0	3	0
Type III cardiology consultation	0	1	3-4 (assumed 3.5)	2	3	0
Hospitalization – exacerbation treatment	1	1-2 (assumed 1.5)	2	1	2-3 (assumed 2.5)	1
Hospitalization – control tests	2	0	1	2	1-2 (assumed 1.5)	0,5
Percentage of patients requiring home oxygen therapy	10%	10%	30-40% (assumed 35%)	0%	80%	17%

3.3 Conventional pharmacological treatment

Conventional treatment used in patients with pulmonary arterial hypertension included all therapeutic groups (diuretics, anticoagulants, digitalis glycosides and calcium channel blockers) listed in guidelines of the European Society of Cardiology concerning pharmacological treatment of this group of patients, see Table 3.

In addition, centre 2 reported use of angiotensin convertase inhibitors (enalapril) in treatment of children with pulmonary arterial hypertension.

Table 3.
Summary of the survey results – use of conventional medications in treatment of PAH at specific centres (mean daily doses given in brackets).

Drug	Centre 1	Centre 2	Centre 3	Centre 4	Centre 5	Centre 6
Furosemide	66% (120 mg)	10% (1-2 mg/kg of body weight – assumed 1.5 mg/kg)	95% (40-100 mg – assumed 70 mg)	100% (80 mg)	18.5% (80 mg)	50% (40-80 mg – assumed 60 mg)
Spironolactone	75% (50 mg)	40% (1-2 mg/kg; >25 kg 25 mg – assumed 30 mg)	90% (100 mg)	100% (25 mg)	32% (25-100 mg – assumed 62.5 mg)	50% (50-100 mg – assumed 75 mg)
Hydrochlorothiazide	25% (25 mg)	10% (1-2 mg/kg >15 years 25-50 mg – assumed 1.5 mg/kg)	0%	0%	0%	0%
Torasemide	0%	0%	40% (10 mg)	0%	1.2% (40 mg)	0%
Chlortalidone	0%	0%	50% (50 mg)	20% (50 mg)	1.2% (25 mg)	0%
Amiloride + hydrochlorothiazide (brand name: Tialorid)	0%	0%	0%	0%	1.2% (25 mg)	0%
Low-molecular-weight heparin	40% (70 mg)	0%	20% (60 mg)	30% (60 mg)	1.2% (60 mg)	10% (1.6 mg/kg)
Unfractionated heparin	0%	0%	0%	0%	0%	10% (10000 IU)
Acenocumarol	40% (3 mg)	20% (0.5-2 mg – assumed 1.25 mg)	80% (2 mg)	70% (2 mg)	72.8% (according to the INR value – assumed 5 mg)	80% (5 mg)
Digoxin 0.25 mg	25% (0.125 mg)	0%	50% (n.d.)	0%	3.7% (0.1 mg)	30% (0.1-0.25 mg – assumed 0.175 mg)
Digoxin 0.1 mg	0%	0%	0%	0%	1.2% (0.1 mg)	0%
Diltiazem	5% (240 mg)	10% (180 mg)	0%	10% (240 mg)	21% (120 mg)	20% (540 mg)
Nifedipine	3% (60 mg)	0%	0%	0%	0%	0%
Amlodipine	0%	0%	0%	0%	0%	10% (7.5 mg)
Verapamil	0%	0%	50% (120-240 mg – assumed 180 mg)	0%	56.2% (240-360 mg – assumed 300 mg)	0%
Enalapril	0%	30% (0.3-1 mg/kg – assumed 0.65 mg/kg)	0%	0%	0%	0%

3.4 Use of novel drugs in treatment of PAH – current practice

Table 4 presents percentages of patients at specific centres, who received novel drugs used in treatment of PAH (mean daily doses are given in brackets). Both drugs administered within clinical trials and those obtained by means of direct import or bought by the patients (without reimbursement) were taken into account.

In total, the most common drug was sitaxsentan (32.9% of patients), mainly due to clinical trials being conducted at the centres. 18.9% of patients were treated with sildenafil (brand name: Revatio or Viagra). Epoprostenol was not used in any of the centres.

Combination treatment, in which at least two of the analysed drugs (from different therapeutic groups) are used at the same time, was required in 9.9% of patients. Combination therapy regimens used at specific centres are presented in Table 5.

None of the surveyed centres reported any serious adverse events associated with use of the analysed drugs.

Table 4.
Summary of the survey results – use of novel drugs in treatment of PAH at specific centres (mean daily doses given in brackets).

	Centre 1	Centre 2	Centre 3	Centre 4	Centre 5	Centre 6
Bosentan	2% (250 mg)	5% (90 mg)	0%	0%	0%	0%
Epoprostenol	0%	0%	0%	0%	0%	0%
Iloprost	5% (6 vials)	0%	9.52% (5 vials)	30%	2.5% (6-9 vials)– assumed 7.5 vials)	25% (n.d.)
Sildenafil	23% (60 mg)	60% (3 mg/kg; >20 kg 60 mg – assumed 60 mg)	0%	10% (50 mg)	20% (60 mg)	80% (n.d.)
Treprostinil	5% (30 ng/kg/min)	0%	3.17% (n.d.)	70% (40 ng/kg/min)	3.7% (10 ng/kg/min)	0%
Sitaxsentan	38% (100 mg)	0%	38% (100 mg)	0%	36% (100 mg)	12.5% (100 mg)
Ambisentan	0%	2% (nd)	0%	0%	0%	0%

Table 5.
Summary of the survey results – used combination therapies.

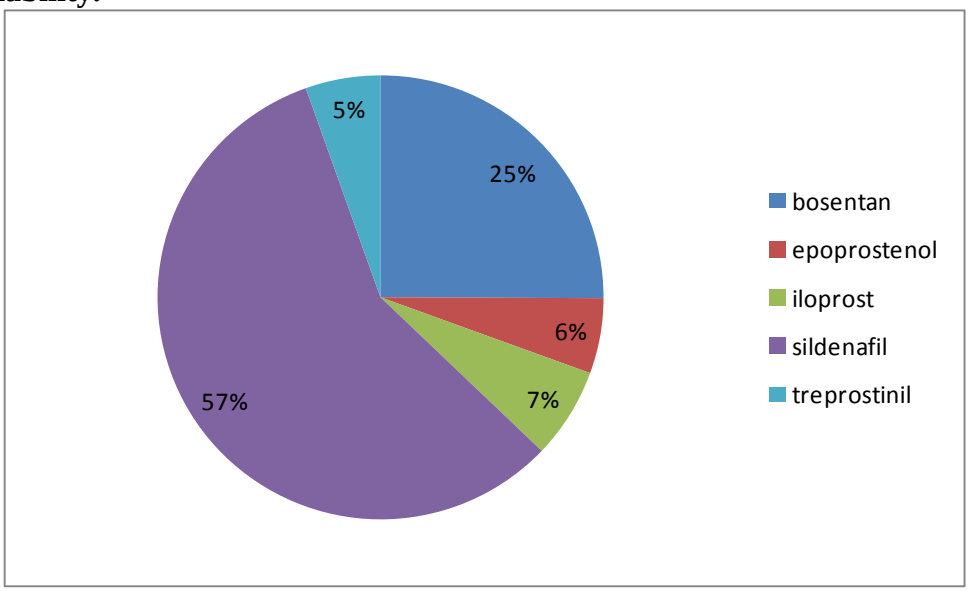
	Centre 1	Centre 2	Centre 3	Centre 4	Centre 5	Centre 6
sildenafil + iloprost	1%	0%	0%	5%	0%	12,5%
sildenafil + treprostinil	2%	0%	0%	5%	2,5%	0%
sildenafil + bosentan	0%	5%	0%	0%	0%	0%
sitaxsentan+treprostinil	1%	0%	5%	0%	0%	0%
sitaxsentan+iloprost	1%	0%	15%	0%	0%	0%

3.5 Expected structure of use of the analysed drugs assuming their unlimited availability

At present availability of novel drugs used in treatment of PAH in Poland is not facilitated by any means (e.g. reimbursement or therapeutic programs); use of specific preparations depends therefore on: direct import, clinical trials, supply of drugs by manufacturers and availability of other preparations, not registered for treatment of PAH, but containing the same active agent. The clinicians were therefore asked, how often – in their opinion, assuming full and unlimited availability of the analysed drugs and taking into account indications, contraindications, adverse effects and tolerance – particular drugs would be used in first-line treatment of pulmonary hypertension. The results are presented in Table 6.

In the opinion of clinicians from the surveyed centres, sildenafil would be the most common first-line drug (57.43% in total) and the second-most common drug would be bosentan (25.04%) (Figure 2).

Figure 2.
Expected structure of use of the first-line drugs assuming their unlimited availability.



Another question was, what the target (i.e. stable in the whole group of patients, regardless of time from diagnosis) structure of use of the analysed drugs would be. Results concerning the target structure of use of the analysed drugs (sildenafil and bosentan still comprising over 80%) are presented in Table 7 and Figure 3.

Figure 3.
Expected target structure of use of the analysed drugs, assuming their full availability (the categories do not sum up to 100% because the survey included combination therapies; a column diagram was therefore used instead of a pie diagram).

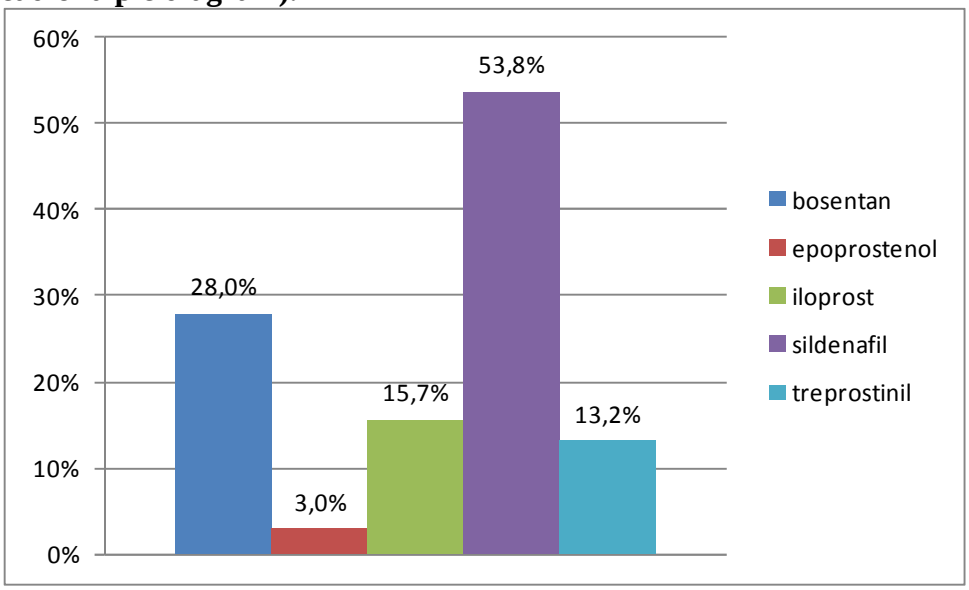


Table 6.
Summary of the survey results – expected structure of use of the first-line drugs assuming full availability of the analysed drugs.

	Centre 1	Centre 2	Centre 3	Centre 4	Centre 5	Centre 6
bosentan	20%	5%	45%	20%	16,7%*	15%
epoprostenol	1%	0%	1%	0%	16,7%*	10%
iloprost	4%	5%	2%	20%	11,1%*	10%
sildenafil	75%	90%	50%	30%	44,4%*	60%
treprostinil	0%	0%	2%	30%	11,1%*	5%
* rescaled so that the sum is 100% (the original sum was 90%);						

Table 7.
Summary of the survey results – expected target structure of use of the analysed drugs

	Centre 1	Centre 2	Centre 3	Centre 4	Centre 5	Centre 6
bosentan	25%	20%	40%	30%	20%	30%
epoprostenol	2%	0%	2%	0%	5%	10%
iloprost	10%	20%	10%	20%	20%	60%
sildenafil	80%	90%	40%	20%	35%	70%
treprostinil	8%	0%	8%	30%	20%	30%

4 FINAL CONCLUSIONS

Since patients with pulmonary arterial hypertension require highly specialist care offered by a small number of clinical centres in Poland, it was possible to survey all these centres and gather complete data for the Polish population.

In this report the whole population of patients with PAH – and not a sample – is investigated; no statistical analysis was therefore performed.

The survey results indicate that prevalence in Poland (8 patients per million) is nearly twice lower than that in France (15 per million); the percentage of patients in NYHA class III or IV is also lower (61% vs. 75%, respectively), [4].

There is no single established regimen of management for patients with PAH (outpatient consultations, control hospitalisations) in Poland; current practice in the surveyed centres is therefore different.

Conventional pharmacological treatment is used in accordance with guidelines of the European Society of Cardiology. However, present situation concerning use of novel (not reimbursed) drugs is a result of the market specificity (direct import, clinical trials).

The survey had certain limitations. It must be noted that prognoses concerning expected structure of use of novel drugs assuming their full availability (both as first-line drugs and with respect to the target structure) are only experts' opinions and should be verified after reimbursement/ therapeutic programs have been introduced.

This analysis reflects the status at a specific time point and therefore does not allow for conclusions concerning incidence of PAH in Polish population or survival time in this group of patients. In this respect, a registry of pulmonary arterial hypertension, kept from 2007 within the POLKARD program, will undoubtedly be helpful [9].

APPENDIX – PEER REVIEW

Final review of the report (17.12.2008 r.):

“Treatment of pulmonary arterial hypertension in Poland – current practice. Survey results”

.Reviewers: Dr Yen-Fu Chen and Dr David Moore

This well presented report describes a survey of Polish centres treating patients with pulmonary arterial hypertension. It clearly and concisely details the content of the survey and the findings. The coverage of all institutions known to have provided specialist care to patients with pulmonary arterial hypertension in Poland ensures that the findings are generalisable at national level. The authors have adequately addressed our comments and have highlighted a few inherent limitations associated with such a survey and this survey in particular.

This is undoubtedly an important piece of work in determining the prevalence, current treatment and possible future utilisation of the interventions under investigation within Poland.

GLOSSARY

analysed drugs – bosentan (Tracleer), epoprostenol (Flolan), iloprost (Ventavis), sildenafil (Revatio), treprostinil (Remodulin)

remaining drugs – conventional treatment of PAH, i.e. anticoagulants, calcium channel blockers, diuretics and digitalis glycosides

treatment regimen – a method of treatment within the new scenario using the analysed drugs, including structure of the first-line drugs as well as probabilities of transition between them and introduction of combination therapies

combination therapy – a therapy, in which at least two of the analysed drugs (from different therapeutic groups) are used at the same time

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