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# Results of European post-marketing surveillance of bosentan in pulmonary hypertension

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**ABSTRACT: After the approval of bosentan for the treatment of pulmonary arterial hypertension (PAH), European authorities required the introduction of a post-marketing surveillance system (PMS) to obtain further data on its safety profile.**

**A novel, prospective, internet-based PMS was designed, which solicited reports on elevated aminotransferases, medical reasons for bosentan discontinuation and other serious adverse events requiring hospitalisation. Data captured included demographics, PAH aetiology, baseline functional status and concomitant PAH-specific medications. Safety signals captured included death, hospitalisation, serious adverse events, unexpected adverse events and elevated aminotransferases.**

**Within 30 months, 4,994 patients were included, representing 79% of patients receiving bosentan in Europe. In total, 4,623 patients were naïve to treatment; of these, 352 had elevated aminotransferases, corresponding to a crude incidence of 7.6% and an annual rate of 10.1%. Bosentan was discontinued due to elevated aminotransferases in 150 (3.2%) bosentan-naïve patients. Safety results were consistent across subgroups and aetiologies.**

**The novel post-marketing surveillance captured targeted safety data (''potential safety signals'') from the majority of patients and confirmed that the incidence and severity of elevated aminotransferase levels in clinical practice was similar to that reported in clinical trials. These data complement those from randomised controlled clinical trials and provide important additional information on the safety profile of bosentan.**

**KEYWORDS: Aminotransferase elevation, bosentan, post-marketing surveillance, pulmonary arterial hypertension**

Due to their very nature, orphan diseases present a particular challenge, not only in terms of drug development but also regarding benefit/risk considerations since the number of patients that can be included in clinical trials is limited. Pulmonary arterial hypertension (PAH), a progressive disease with a traditionally poor prognosis [1, 2], is no exception.

Endothelin (ET) is one of the mediators implicated in the pathogenesis of PAH [3]. In 2002, bosentan, an orally administered dual $ET_A/ET_B$ receptor antagonist, received orphan drug status and marketing authorisation in the USA and in Europe after two randomised controlled trials demonstrated its safety and efficacy in ~250 patients [4, 5]. However, abnormal liver function tests occurred in 12.8% of patients who had been exposed to bosentan. In all instances recorded during the bosentan clinical development programme, aminotransferases returned to pre-treatment levels without sequelae within a few days to 9 weeks, either spontaneously or after dose reduction or discontinuation. Nevertheless, concerns remained regarding the potential of bosentan to cause severe or permanent liver damage, especially since the overall experience with this drug was based on only 59 patient-yrs at the time of approval.

For these reasons, the European Medicines Agency (EMEA) required the initiation of a post-marketing surveillance (PMS) programme, Tracleer® (Actelion Pharmaceuticals Ltd, Allschwil, Switzerland) PMS, in European countries prior to the market introduction of bosentan [6]. The aims of Tracleer® PMS were three-fold: 1) education of practitioners on the appropriate use of bosentan and encouragement of the reporting of adverse drug reactions (ADR); 2) collection of potential safety signals, including

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the incidence of elevated liver aminotransferase levels during bosentan treatment in clinical practice; and 3) assessment of the practicality and appropriate use of the algorithm developed in registration studies for managing aminotransferase elevations in daily clinical practice, including the re-introduction of bosentan where appropriate.

The present study reports data from this PMS programme related to the use of bosentan in PAH patients.

## METHODS

### *Design*

Tracleer® PMS was a European noninterventional, prospective, internet-based PMS database set up in May 2002 in 18 countries (Austria, Belgium, Cyprus, Denmark, France, Finland, Germany, Greece, Iceland, Ireland, Italy, Luxemburg, the Netherlands, Norway, Portugal, Sweden, Spain, UK). Prescribers of bosentan, identified through the controlled distribution of the drug, were invited to participate on a voluntary basis and were educated on the use of the drug for the treatment of PAH.

#### Education

Before an individual patient could be prescribed bosentan, written certification had to be provided by the prescriber stating that: 1) bosentan was being prescribed for a medically appropriate use in the treatment of PAH, as described in the full prescribing information; and 2) the prescriber had reviewed the liver and pregnancy warnings with the patient and had committed to undertaking the appropriate monitoring of liver function tests and pregnancy tests (if the patient was female and of child-bearing potential). At the first visit, the system alerted the prescriber, by means of a pop-up window, to potential contraindications of bosentan as outlined in the summary of product characteristics (including pregnancy and baseline values of liver aminotransferases >3 × the upper limit of normal (ULN)).

#### Data collection

Once registered as users, practitioners were requested to enter patient data into the web-based system on a regular basis. Descriptive data were obtained and included demographics, aetiology, New York Heart Association (NYHA) functional class at baseline and use of concomitant PAH-specific medication. This information was directly transferred *via* a secure internet connection to a central database. Aggregated data were reviewed weekly by Actelion's Global Drug Safety (GDS) department to determine whether safety signals were present. This process is summarised in figure 1.

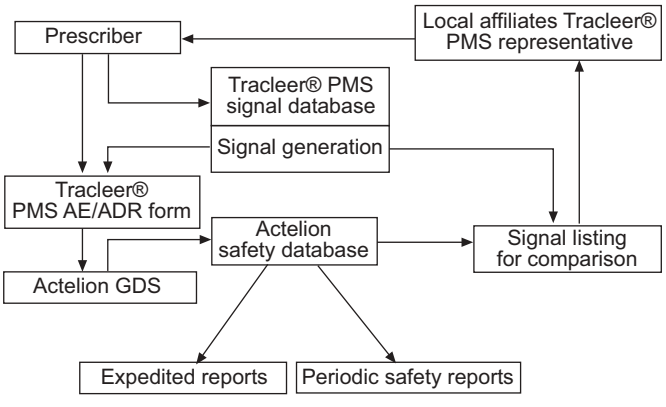


**FIGURE 1.** Tracleer® (Actelion Pharmaceuticals Ltd, Allschwil, Switzerland) post-marketing surveillance (PMS) data processing flow chart. AE: adverse event; ADR: adverse drug reaction; GDS: Global Drug Safety.

Signals were grouped as potentially safety-related or nonsafety-related. Potential safety signals were defined as: death; hospitalisation; pregnancy; serious adverse event (AE)/ADR; ADR not listed in the summary of product characteristics (SPC); elevations of aminotransferase levels; other abnormal laboratory values; transplantation; atrial septostomy; or initiation of *i.v.* prostacyclin. Nonsafety signals were defined as reasons for discontinuation, such as patient request, loss to follow-up or nonmedical reasons.

Notifications as to whether any further information was required on the case were automatically provided in real time to the person entering data. Data classified as potential safety signals at the time of web-based entry resulted in an immediate prompt to the prescriber, *via* a pop-up window, to complete an AE/ADR form, which was forwarded to the GDS department and entered into the safety database. If, despite prompting and follow-up attempts, an AE/ADR form was not completed, the minimal information from the potential safety signal was entered into the safety database without the receipt of an official form when it met all four regulatory criteria for defining an AE.

The denominator for the percentage of bosentan-treated patients in Europe enrolled in the Tracleer® PMS system was determined from the distributors in the participating countries who had accurate records on the numbers of bottles of drug supplied monthly to pharmacies and from the close communication with prescribers identified through controlled distribution. The analyses for this report were only performed on data from bosentan-naïve patients in the Tracleer® PMS system as a conservative approach, since patients already receiving bosentan may have represented a skewed patient population with less likelihood of safety signals, as their treatment had been ongoing for some time.

Elevations in liver aminotransferase levels were defined as an increase in levels of alanine- or aspartate-aminotransferase (ALT or AST, respectively) of >3 × ULN. The algorithm for management of ALT/AST elevations is presented in table 1. The management of patients with an elevation in aminotransferase levels was followed by Actelion GDS until stabilisation or resolution.

Liver disorders were reported in the Tracleer® PMS system and followed up by Actelion GDS on a case-by-case basis to evaluate whether they met the criteria for serious drug-induced liver injury. Serious drug-induced liver injury, according to Hy's Law [7], has been defined as: ALT/AST elevations >3 × ULN accompanied by serum total bilirubin elevation of >3 × ULN or visible jaundice, without evidence of biliary obstruction (without significant elevation of alkaline phosphatase). All cases were reviewed by an International Liver Safety Board (ILSB) of independent experts.

**TABLE 1** European Union summary of product characteristics (SPC) algorithm for the management of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations

| Liver function | Treatment and monitoring recommendations |
|---|---|
| **Before treatment** | Liver ALT/AST levels must be measured prior to initiation of treatment and subsequently at monthly intervals. In addition, levels must be measured 2 weeks after any dose increase |
| ALT/AST levels | |
| >3–⩽5×ULN | Confirm by another liver test; if confirmed, reduce daily dose or stop treatment and monitor ALT/AST levels at least every 2 weeks. If ALT/AST levels return to pre-treatment values, consider continuing or re-introducing bosentan according to re-introduction conditions[¶] |
| 5–⩽8×ULN | Confirm by another liver test; if confirmed, stop treatment and monitor ALT/AST levels at least every 2 weeks. If ALT/AST levels return to pre-treatment values, consider continuing or re-introducing bosentan according to re-introduction conditions[¶] |
| >8×ULN | Treatment must be stopped and re-introduction of bosentan is not to be considered |
| **Associated clinical symptoms of injury[#]** | Treatment must be stopped and re-introduction of bosentan is not to be considered |

ULN: upper limit of normal. [#]: *i.e.* nausea, vomiting, fever, abdominal pain, jaundice, unusual lethargy or fatigue or flu-like syndromes (arthralgia, myalgia, fever); [¶]: re-introduction of treatment with bosentan should only be considered if the potential benefits outweigh the potential risks and when liver ALT/AST levels are within pre-treatment values. The advice of a hepatologist is recommended. Re-introduction must follow the prescribing guidelines detailed in the SPC. ALT/AST levels must be checked within 3 days of re-introduction, again after a further 2 weeks and thereafter according to the above recommendations.

### *Analyses*

Analysis was purely observational. Crude rate calculation of aminotransferase elevations was based on the actual number of events reported (numerators) and the number of exposed patients (denominators), but must be viewed in the context of exposure time to bosentan. The rate of aminotransferase elevation was based on the 4,623 patients who were naïve to bosentan treatment at the time of database entry. Of these 4,623 bosentan-naïve patients, 19 were reported to have elevated aminotransferase levels (>3×ULN) at baseline, seven of whom had aminotransferase elevation following bosentan initiation and were included in the analysis. The annual rate (event rate·yr$^{-1}$) was obtained by fitting an exponential distribution to the observed data using the method of maximum likelihood. The incidence of discontinuation of bosentan due to elevated aminotransferases and the proportion of patients in whom bosentan was re-introduced following temporary withdrawal were calculated based on the number at risk because of an elevation of aminotransferases.

## RESULTS

### *Baseline characteristics*

Between May 2002 and November 2004, a total of 17 countries enrolled 4,994 patients who had been treated with bosentan under clinical practice conditions and whose data were captured in the database; this represents 79% of the 6,318 patients who had received bosentan in Europe during that period. In total, 4,623 (93%) out of the 4,994 patients were naïve to bosentan at database entry. The total exposure to bosentan was 3,416 patient-yrs. The baseline characteristics of the bosentan-naïve patients are given in table 2.

### *Concomitant medication*

A large majority of patients (72.7%) were receiving concomitant anticoagulants at baseline. The presence of patients receiving concomitant therapy with sildenafil (2.6%) or prostanoids (16.2%) at baseline (table 2) resulted in additional subpopulations, which allowed analysis of the safety of bosentan in combination with these drugs.

### *Potential safety signals*

Potential safety signals were noted in 1,625 (35.2%) out of the 4,623 patients; the incidence was consistent across the different subpopulations as shown in table 3.

Elevated aminotransferases were reported in 352 patients, giving a crude incidence of 7.6%, corresponding to an annual rate of 10.1% (table 4). The Kaplan–Meier estimates of time to the first aminotransferase elevation in the bosentan-naïve patient population (n=4,623) is shown in figure 2. There was little variation in the annual rate of occurrence of elevated aminotransferases across subpopulations. Exceptions include a higher incidence in patients reported as having PAH secondary to mixed connective tissue disease and a lower incidence in paediatric patients (aged 2–11 yrs) and those patients with PAH associated with congenital heart disease. The rates of occurrence of elevated aminotransferases in patients receiving concomitant treatment with sildenafil or prostanoids at baseline were no higher than those observed in the overall patient population.

A breakdown of the magnitude of aminotransferase elevations in the 352 bosentan-naïve patients at database entry is shown in table 5; elevations ranging >3–⩽5×ULN were the most common.

In the 352 patients with elevated aminotransferases, bosentan was continued in 134 patients and re-introduced following temporary withdrawal in a further 45 patients of whom 31 were maintained on therapy, resulting in treatment continuation in a total of 165 (47%) patients. Out of the 352 patients, 150 were withdrawn from therapy due to elevated liver aminotransferases, representing 3.2% of the total bosentan-naïve population (fig. 3).

At bosentan therapy initiation, there were 2,877 patients receiving oral anticoagulants (table 4). Out of these, nine

**TABLE 2** Baseline (BL) characteristics of patients enrolled in Tracleer® post-marketing surveillance (PMS) who were naïve to bosentan treatment at the time of database entry

| | Subjects n | Age yrs | Female | NYHA Functional class | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | I | II | III | IV | Unknown |
| **All bosentan-naïve patients** | 4623 | 52±18.8 | 67.1 | 1.7 | 11.8 | 67.8 | 13.6 | 5 |
| **Patients aged <2 yrs** | 23 | 0.6±0.5 | 26.1 | 8.7 | 21.7 | 26.1 | 21.7 | 21.7 |
| **Patients aged 2–11 yrs** | 146 | 6.9±3.1 | 48.6 | 6.2 | 28.1 | 50.7 | 10.3 | 4.8 |
| **Patients aged ⩾12 yrs** | 4443 | 54.5±16.8 | 67.9 | 1.5 | 11.3 | 68.6 | 13.7 | 4.8 |
| **Subgroups according to aetiology** | | | | | | | | |
| Idiopathic PAH | 1583 | 51.7±19.4 | 63.3 | 1.6 | 11.2 | 72 | 12.1 | 3.2 |
| PAH-scleroderma | 1017 | 60.7±12.5 | 84 | 2.7 | 13 | 64.3 | 12.2 | 7.9 |
| PAH-mixed connective tissue disease | 121 | 54.9±14.9 | 82.6 | 0 | 9.1 | 65.3 | 19.8 | 5.8 |
| PAH-lupus | 100 | 47±15.4 | 90 | 2 | 17 | 69 | 7 | 5 |
| PAH-congenital heart disease | 579 | 34.2±18.6 | 65.3 | 0.9 | 16.4 | 67.7 | 10.9 | 4.1 |
| PAH-HIV | 102 | 40.8±6.3 | 39.2 | 3.9 | 14.7 | 66.7 | 7.8 | 6.9 |
| CTEPH | 470 | 61.6±13.7 | 60.9 | 1.1 | 8.5 | 72.3 | 16.2 | 1.9 |
| PH-pulmonary fibrosis[#] | 85 | 60.6±15.4 | 47.1 | 1.2 | 2.4 | 61.2 | 28.2 | 7.1 |
| Portopulmonary hypertension | 82 | 53.2±14.5 | 51.2 | 1.2 | 12.2 | 67.1 | 13.4 | 6.1 |
| PH-other | 461 | 54.9±19.3 | 55.5 | 2.0 | 10.4 | 60.1 | 22.1 | 5.4 |
| **Subgroups according to concomitant medication** | | | | | | | | |
| Sildenafil at BL | 119 | 35.7±25.2 | 57.1 | 1.7 | 11.8 | 55.5 | 25.2 | 5.9 |
| Prostanoids at BL | 751 | 47.8±18.7 | 72 | 3.3 | 15 | 62.2 | 16.4 | 3.1 |
| Oral anticoagulants at BL | 2,877 | 54.2±17.2 | 66.3 | 1.3 | 10.2 | 71.5 | 14.5 | 2.5 |
| Not receiving oral anticoagulants[¶] | 1514 | 49.6±21.4 | 68.2 | 2.6 | 15 | 60.4 | 12.3 | 9.8 |

Data are presented as mean±SD or %, unless otherwise stated. There were 24 patients to which no aetiology was assigned and no date of birth was available for 11 patients. NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; PH: pulmonary hypertension. [#]: 1 patient had CTEPH and PH-pulmonary fibrosis; [¶]: for the duration of PMS.

patients were reported to meet Hy's Law [7] criteria for serious drug-induced liver injury. Additionally, one patient also met the criteria after oral anticoagulant medication was initiated during bosentan treatment. Out of these 10 patients, four died. All causes of death were considered unrelated to liver function abnormalities (*e.g.* sepsis, disease progression) after clinical

**TABLE 3** Potential safety signals

| | All patients | Patient subgroups | | | |
|---|---|---|---|---|---|
| | | Idiopathic PAH | PAH-SSc | PAH-CHD | Paediatric 2–11 yrs |
| **Subjects n** | 4623 | 1583 | 1017 | 579 | 146 |
| **⩾1 safety signal[#]** | 33.2 | 36.7 | 34.4 | 19.7 | 30.8 |
| **Death** | 9.1 | 9.2 | 11.4 | 4.7 | 7.5 |
| **Need for transplantation/atrial septostomy** | 1.0 | 1.7 | 0.3 | 1.0 | 0.7 |
| **Hospitalisation** | 4.1 | 3.5 | 5.0 | 2.6 | 4.8 |
| **Need for *i.v.* prostacyclin or equivalent** | 2.1 | 2.5 | 2.3 | 1.4 | 1.4 |
| **Abnormal ALT/AST after baseline** | 7.6 | 8.4 | 9.4 | 2.8 | 2.7 |
| **Other abnormal laboratory value** | 2.5 | 2.3 | 3.9 | 0.7 | 1.4 |
| **ADR not in SPC** | 1.3 | 1.5 | 1.5 | 1.2 | 4.8 |
| **Other adverse events** | 6.2 | 6.5 | 6.7 | 2.8 | 7.5 |
| **Other reason for discontinuation** | 4.4 | 3.6 | 2.9 | 3.8 | 4.1 |

Data are presented as %, unless otherwise stated. PAH: pulmonary arterial hypertension; SSc: scleroderma; CHD: congenital heart disease; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ADR: adverse drug reaction; SPC: summary of product characteristics. [#]: patients may have had >1 potential safety signal.

**TABLE 4** Frequency of elevated aminotransferases according to subgroups

| | Subjects n | Exposure yrs | Elevated aminotransferases | |
|---|---|---|---|---|
| | | | Crude rate | Annual rate |
| **All bosentan-naïve patients** | 4623 | 0.57; 0.74±0.63 | 7.6 | 10.1 |
| **Patients aged <2 yrs[#]** | 23 | 0.17; 0.41±0.65 | 4.3 | |
| **Patients aged 2–11 yrs** | 146 | 0.56; 0.69±0.58 | 2.7 | 3.9 |
| **Patients aged ⩾12 yrs** | 4443 | 0.57; 0.75±0.63 | 7.8 | 10.3 |
| **Subgroups according to aetiology** | | | | |
| Idiopathic PAH | 1583 | 0.68; 0.84±0.69 | 8.4 | 10 |
| PAH-scleroderma | 1017 | 0.55; 0.73±0.60 | 9.4 | 12.7 |
| PAH-mixed connective tissue disease | 121 | 0.47; 0.69±0.61 | 16.5 | 23.5 |
| PAH-lupus | 100 | 0.69; 0.84±0.67 | 10 | 10.7 |
| PAH-congenital heart disease | 579 | 0.57; 0.74±0.62 | 2.8 | 3.8 |
| PAH-HIV | 102 | 0.64; 0.74±0.59 | 8.8 | 12.1 |
| CTEPH | 470 | 0.52; 0.65±0.56 | 5.5 | 8.4 |
| PH-pulmonary fibrosis[¶] | 85 | 0.33; 0.43±0.41 | 3.5 | 8.2 |
| Portopulmonary hypertension | 82 | 0.50; 0.66±0.56 | 4.9 | 5.6 |
| PH-other | 461 | 0.37; 0.58±0.57 | 7.6 | 12.5 |
| **Subgroups according to concomitant medication** | | | | |
| Sildenafil at BL | 119 | 0.34; 0.58±0.56 | 7.6 | 12 |
| Prostanoids at BL | 751 | 0.51; 0.74±0.65 | 7.2 | 9.5 |
| Oral anticoagulants at BL | 2877 | 0.64; 0.80±0.66 | 8.0 | 10.2 |
| Not receiving oral anticoagulants[+] | 1514 | 0.40; 0.58±0.56 | 5.2 | 8.6 |

Data are presented as median; mean±SD or %, unless otherwise stated. There were 24 subjects for which no aetiology was assigned to 24 patients and no date of birth was available for 11 patients. PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; PH: pulmonary hypertension; BL: baseline. [#]: could not be computed as numbers too small for evaluation; [¶]: 1 patient had CTEPH and PH-pulmonary fibrosis; [+]: for the duration of the post-marketing surveillance.

case review by the ILSB. There was no permanent or fatal liver injury associated with the use of bosentan in any of the patients enrolled in the Tracleer® PMS system.

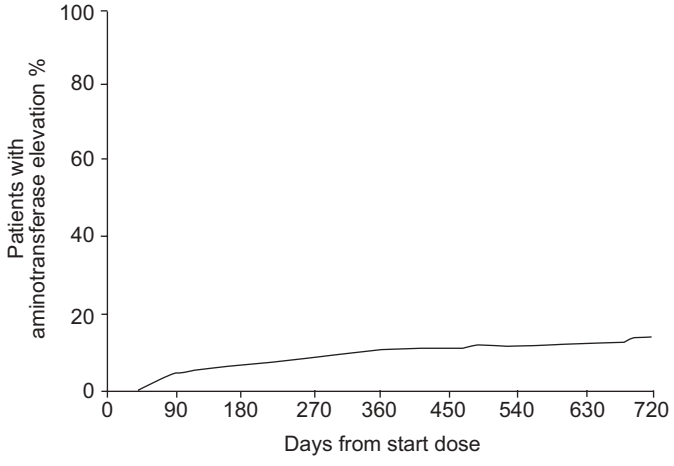


**FIGURE 2.** Kaplan–Meier estimates of time to first elevation of aminotransferases. The number of subjects was 4,623, 3,226, 2,387, 1,799, 1,346, 1,008, 697, 397 and 203 for 0, 90,180, 270, 360, 450, 540, 630 and 720 days from the start dose, respectively.

### *Discontinuations for any reason*

Discontinuations occurred in a total of 1,286 (27.8%) out of the 4,623 patients. The most common reasons for discontinuation were death (9.1%) and hospitalisation (4.1%; mainly due to clinical worsening of PAH); other reasons included the need for *i.v.* prostacyclin, transplantation or atrial septostomy, other abnormal laboratory values, loss to follow-up, patient request to discontinue or nonmedical reasons.

**TABLE 5** Magnitude of elevations in previously bosentan-naïve patients who experienced aminotransferase elevations

| Magnitude of elevation | Patients[#] |
|---|---|
| **⩽3×ULN** | 17 (0.4) |
| **>3–⩽5×ULN** | 130 (2.8) |
| **>5–⩽8×ULN** | 57 (1.2) |
| **>8×ULN** | 62 (1.3) |
| **Unknown** | 86 (1.9) |
| **Total** | 352 (7.6) |

Data are presented as n (%). ULN: upper limit of normal. [#]: percentage of all patients naïve to bosentan therapy (n=4,623).

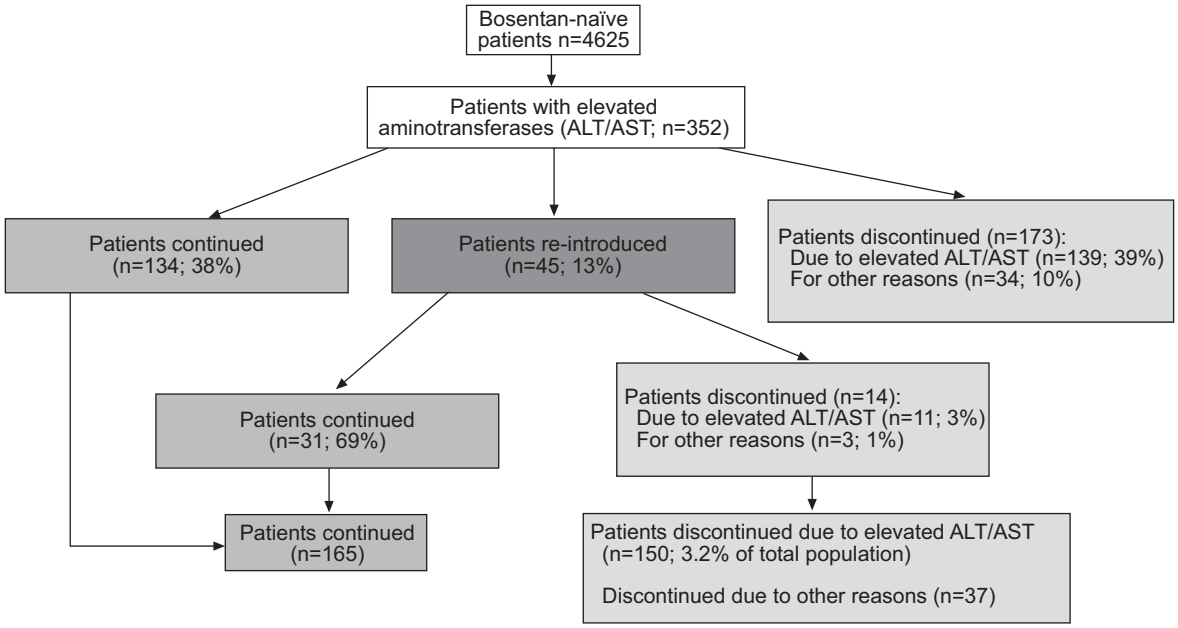


**FIGURE 3.** Management of patients with elevated liver aminotransferases. ALT: alanine aminotransferase; AST: aspartate aminotransferase.

## DISCUSSION

As of November 2004, nearly 5,000 pulmonary hypertension patients across Europe were included in the Tracleer® PMS system, representing 79% of patients receiving bosentan at that time. The calculated exposure to bosentan represented 3,416 patient-yrs, a >50-fold increase over the 59 patient-yrs of experience from the two pivotal trials [4, 5]. A total of 4,623 patients were naïve to bosentan treatment and, of these, 352 had elevated liver aminotransferases, corresponding to a crude incidence of 7.6% and an annual rate of 10.1%, which was consistent with the crude rates observed in the two pivotal trials of bosentan (12.8%) and in the eight placebo-controlled bosentan trials included in the safety assessment and registration submission (11.2%) [4, 5, 8]. Bosentan was discontinued due to elevated aminotransferase levels in 150 patients, representing 3.2% of all bosentan-naïve patients. The incidence of elevated aminotransferases was similar in most subgroups although higher in patients with PAH secondary to mixed connective tissue disease and lower in paediatric patients and those with PAH associated with congenital heart disease. The significance of these findings is unclear since these subgroups included fewer patients than the larger subgroups of idiopathic PAH or PAH associated with scleroderma. As expected, the database included only very few patients (n=19) with baseline aminotransferase elevations $>3 \times$ ULN, since such levels of aminotransferases are contraindications to therapy according to the SPC. No aminotransferase elevations were reported for the majority (n=12) of these patients during bosentan treatment.

The Tracleer® PMS system was initiated with the following objectives: 1) education of practitioners on the appropriate use of bosentan and encouragement of the reporting of ADR; 2) collection of safety signals, including the incidence of elevated aminotransferase levels during bosentan treatment in clinical practice; and 3) assessment of the practicality and appropriate use of the algorithm managing aminotransferase elevations in daily clinical practice.

Independent of the Tracleer® PMS system, the distribution system in place for bosentan enabled accurate assessment of the incidence of elevated liver aminotransferases by providing an accurate count of the number of patients in the EU receiving bosentan and ensured that physicians did not prescribe bosentan unless appropriately educated regarding the possibility of aminotransferase elevations.

Liver aminotransferase elevations, a class effect of all endothelin receptor antagonists, represent a potential safety risk. The design of the Tracleer® PMS system ensured that prescribers were aware of this necessity and prompted to report potential safety signals [6]. The Tracleer® PMS system allowed the evaluation of safety data from a broad range of patients in daily clinical practice, including those from various aetiologies and those receiving concomitant PAH-specific medications, for which a number of practical and clinically relevant safety issues can be addressed. Compared with clinical trial data [4, 5], no new safety signals emerged in the overall population or in the various subgroups. Most aminotransferase elevations occurred during the first 6 months of treatment, and after 1 yr the probability of developing elevated aminotransferases was greatly reduced. This observation reinforces the need for monthly monitoring of liver aminotransferases for the duration of bosentan treatment. The incidence of aminotransferase elevations was comparable in patients with or without concomitant oral anticoagulants. Notably, patients with portopulmonary hypertension, who may be considered to be more susceptible to liver injuries, did not experience a higher rate of aminotransferase elevations than other subgroups. This supports an earlier report, which suggests that bosentan can be safely administered in patients with cirrhosis who have well preserved liver function [9].

The extensive database facilitated assessment of the suitability of the algorithm developed in a clinical trial setting to manage aminotransferase elevations and thereby prevent serious and irreversible liver injury in a large diverse population of patients. In many cases where elevations of aminotransferases were reported, patients were successfully managed and the use of the algorithm allowed for the successful re-introduction or continuation of bosentan in nearly half of those patients. There was no permanent or fatal liver injury associated with the use of bosentan, supporting use of the algorithm.

One difference from the findings in clinical trials and the data generated by the Tracleer® PMS system was that a higher proportion of patients discontinued treatment due to elevated aminotransferases compared with that observed in the pivotal clinical trials of bosentan [4, 5]. In the pivotal studies, 1.8% of patients discontinued due to aminotransferase elevations, compared with 3.2% of patients in the Tracleer® PMS database, indicating that patients followed in the Tracleer® PMS system may have been discontinued more readily from treatment than patients in the clinical trial setting, or that patients treated for longer with bosentan in the post-marketing setting still had the potential to develop aminotransferase elevations, albeit at a lower rate.

Due to the nature of the system, there were a number of inherent limitations. Not all patients treated in Europe were included in the system, since it was voluntary for physicians to participate. Data were not checked against source documents for completeness or accuracy, so any missing or erroneous data would not be identified and corrected, as would be the case in a randomised controlled trial. Assessments were left to the judgement of the investigator, potentially leading to between-centre differences, particularly with respect to subjective measures, such as NYHA functional class assessment at baseline. Adherence to the recommended algorithm for managing elevated aminotransferase levels was not monitored on a case-by-case basis and no alternative algorithm was tested to provide a comparison. Hence, the level of adherence to the algorithm cannot be determined, nor is it possible to conclude that this algorithm is the optimum approach to managing elevated aminotransferase levels. In addition, although education of practitioners on the appropriate use of bosentan was one of the key aims of the system, the level of knowledge was not measured and so it is not possible to conclude whether or not this aim was achieved.

However, the majority of patients prescribed bosentan were included in the database and reporting of potential safety signals was substantially (more than three-fold) higher than reliance on spontaneous reporting of ADR from the non-enrolled population. Ultimately, no new safety signals were discovered, and the rate of occurrence and severity of elevated aminotransferases observed in Tracleer® PMS, with 3,416 patient-yrs of treatment, matched that originally seen in the clinical trial setting, with 59 patient-yrs of treatment [4, 5].

After enrolling nearly 5,000 patients in 2.5 yrs, the EMEA allowed the discontinuation of the Tracleer® PMS programme, agreeing that it had fulfilled its objectives. This novel programme, using real-time internet support, proved useful in tracking and clarifying safety concerns relating to the use of therapy outside the realm of the controlled clinical trial setting.

In conclusion, the data from the Tracleer® PMS system represent the experience of real life use of bosentan in daily clinical practice and have expanded and affirmed the previously existing data gained from the more controlled clinical trial setting. While data collection was less rigorous than in the clinical trial setting, this system did facilitate collection of more extensive data and data on greater numbers of patients than would have been expected from the usual spontaneous reporting system for AE. This increased level of reporting may well be a result of the monthly prompts to prescribers to regularly monitor liver aminotransferase levels and to report elevations in these levels or other safety signals.

### *Summary*

Data from the Tracleer® post-marketing surveillance system, therefore, complement the data from randomised controlled clinical trials and provide important additional information for prescribers in assessing the risks associated with the use of bosentan in patients with pulmonary hypertension.

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