



Tracking Form for Applicants for New Technology Add-on Payments under the Acute Inpatient Prospective Payment System (IPPS) for Federal Fiscal Year (FY) 2010

1. Technology Name:

SuperSaturatedOxygen Therapy (SSO₂)

2. Manufacturer Name:

TherOx Inc., 17500 Cartwright Rd., Suite 100, Irvine, Ca 92614

3. Trade Brand of Technology

Downstream System

4. Brief Description of Service or Device

SuperSaturatedOxygen Therapy (SSO₂) utilizing the TherOx Downstream System is a novel therapy designed to ameliorate progressive myocardial necrosis by minimizing microvascular damage in AMI patients following percutaneous intervention with coronary stent placement. SSO₂ Therapy refers to the creation and focal delivery of SuperOxygenated arterial blood directly to reperfused areas of myocardial tissue which may be at risk. The net effect of SSO₂ Therapy is to reduce infarct size and thus preserve heart muscle. The TherOx DownStream System is the console portion of a disposable cartridge-based system that withdraws a small amount of the patient's arterial blood and mixes it with a small amount of saline, supersaturated with oxygen, to create highly oxygenenriched blood. The SuperOxygenated blood is delivered directly to the infarct-related artery via the TherOx infusion catheter. SSO₂ Therapy is a cath lab- based procedure. Additional time in the cath lab area is an average of 100 minutes. Therapy duration is 90 minutes and an additional 10 minutes post-procedure preparation for transfer time.

New Criteria

Note: To qualify for a new technology add-on payment, the technology or service must not be reflected in the data used to establish the diagnosis groups (DRGs).

5. Date of Food and Drug Administration (FDA) approval (or expected approval) for the device or service:

Approval is expected in Q2, 2009.

6. Was the product available on the market immediately after FDA approval? If not, please provide the date that the medical service or technology came on the market (i.e., first sales or availability) and an explanation for any delay (i.e., manufacturing issues, shelf life concerns or other reasons.)

(For the complete application requirements, please see the instructions at http://www.cms.hhs.gov/AcuteInpatientPPS/08_newtech.asp#TopOfPage--.

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N/A

7. Does the technology have an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) procedure code(s) or is an application pending?
- a. If yes, please provide the ICD-9-CM procedure code(s) used to identify the clinical procedures(s) with which the medical service and technology is used.

ICD-9-CM CODE: 00.49 SUPERSATURATED OXYGEN THERAPY

- b. If there is no existing ICD-9-CM code that captures this new technology, please indicate whether you will be applying for a new code. (Refer to http://www.cms.hhs.gov/ICD9ProviderDiagnosticCodes/01_overview.asp#TopOfPage for more information.) We note that, if the product were to receive add-on payment status approval, it would need to be distinctly identifiable by ICD-9-CM code(s) in the MedPAR claims data in order to receive add-on payment.

N/A

8. Have you submitted an application of outpatient pass-through payments under the Medicare outpatient prospective payment system? If so, please provide the tracking number, or, if it was approved, please provide the date of approval. (Please refer to http://www.cms.hhs.gov/HospitalOutpatientPPS/04_passthrough-payment.asp#TopOfPage for more information.)

N/A –Hospital inpatient procedure performed in the cath lab.

Cost Criteria

Note: To qualify for a new technology add-on payment, the technology or service must result in average charges for cases using the technology in excess of the lesser of 75 percent of the standardized amount increased to reflect the difference between costs and charges or 75 percent of 1 standard deviation beyond the geometric mean standardized charge for all cases in the DRGs to which the new technology is assigned. Table 10 from the annual final rule lists the thresholds by DRG. The most recent version of Table 10 can be downloaded at: http://www.cms.hhs.gov/AcuteInpatientPPS/08_newtech.asp#TopOfPage.

Provide the following information to demonstrate the technology or service meets the criterion.

9. What is the anticipated average standardized charge per case involving this new technology? For details how to standardize charges please refer to the technical appendix of the application form.

TherOx considers this as proprietary information not available for public disclosure. Cost information is provided in the application to CMS for New Technology Add-On Payment.

10. What is the total estimated cost per case for the service or technology (this will include all costs involved in the case, including the cost of the service or device)? What is the cost of the technology per patient? Please provide a breakdown how the cost of the technology is calculated (i.e., **Drugs** – Average dosage

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or number of units per patient (ml/kg/hr); **Devices** – breakdown of the cost of all components used in the new technology, clearly showing which components are the “new” ones).

TherOx considers this as proprietary information not available for public disclosure. Cost information is provided in the application to CMS for New Technology Add-On Payment.

11. List the diagnosis-related groups (DRGs) to which cases involving this new technology will most likely be assigned.

The CMS Procedure Code ICD-9-CM-00.49 would map SuperSaturated Oxygenation Therapy to MS DRG's 246-249.

12. What is the anticipated volume of Medicare cases involving this technology in FY 2009 (by DRG)?

TherOx considers this as proprietary information not available for public disclosure. Information is provided in the application to CMS for New Technology Add-On Payment.

Clinical Improvement

Note: To qualify for a new technology add-on payment, the technology or service must represent a substantial clinical improvement over existing technologies or services.

13. Please provide a short synopsis of the following clinical issues added to the new technology. Use the regular application to submit full details.

- a. Briefly describe how the new service or technology represents a substantial clinical improvement over existing services or technologies.

The standard of care for the treatment of acute myocardial infarction (AMI) involves the revascularization of the blocked coronary artery by means of either thrombolytic therapy or percutaneous coronary intervention (PCI) with stent placement, accompanied by the administration of adjunctive pharmacologic agents such as antiplatelet drugs and glycoprotein IIb/IIIa inhibitors. In spite of many advances and refinements in PCI for re-opening the blocked coronary artery, AMI patients are at high risk for reduced quality of life, heart failure, and higher mortality, as a result of the extent of necrosis experienced in the myocardium during the infarction. TherOx's SuperSaturated Oxygen Therapy (SSO₂ Therapy) provides an adjunctive treatment option administered immediately after PCI that has demonstrated superiority over PCI alone in reducing infarct size for high-risk anterior AMI patients treated within six hours of symptom onset.

SuperSaturated Oxygen Therapy provides an infusion of oxygen-enriched blood to the target coronary artery through an infusion catheter that is placed in the vessel following successful PCI. This oxygen-enriched, or hyperoxemic blood, has an elevated pO₂ level of 760 – 1000 mmHg, a nearly ten-fold increase over physiologic levels. The mechanism of action of SSO₂ Therapy is believed to be two-fold: first, the increased oxygen levels act to re-open the microcirculatory system within the infarct zone, which has experienced ischemia during the occlusion period. Second, once opened, the blood flow contains additional oxygen to re-start metabolic processes within the stunned myocardium. The net result is to reduce the infarct size, or extent of necrosis, in the myocardium post-AMI, and thus improve left ventricular function. This has been proven definitively in the IDE-sanctioned Acute Myocardial Infarction with Hyperoxemic Therapy II (AMIHOT II) clinical trial.

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Results from the prospective, randomized AMIHOT II study demonstrates the superiority of SSO₂ Therapy to reduce infarct size in this AMI population, with no increased incidence of 30-day Major Adverse Cardiac Events (MACE) as tested in formal safety endpoint analysis. The AMIHOT II study results demonstrated efficacy of SSO₂ Therapy in reducing median infarct size from 26.5% of the left ventricle in the Control group to 20.0% in the SSO₂ group, an absolute reduction of 6.5%. The Bayesian posterior probability of superiority is 96.9%, successfully achieving the study endpoint. In the AMIHOT II study, this finding demonstrates study efficacy success with a magnitude of difference = 6.5%, this magnitude of infarct size reduction has been correlated with both short (< 30 days) and late (> 30 days) mortality reductions in larger AMI clinical trials^{1,2}. In addition, SSO₂ was found to be statistically non-inferior (equivalent) to PCI alone in the prevalence of 30-day MACE (SSO₂ and Control observed rates were 5.4 and 3.8%), within a safety delta of 6%.

- b. List all published peer-review articles relevant to the new service or technology.

Below is a list of publications enclosed with the New Tech application (*note: the therapy was formerly referred to as Aqueous Oxygen, or AO Therapy; this older term appears in the published literature*):

Bartorelli AL. Hyperoxemic perfusion for treatment of reperfusion microvascular ischemia in patients with myocardial infarction. *Am J Cardiovasc Drugs* 2003; 3(4):253-263.

Brereton GJ *et al.* Nucleation in small capillary tubes. *Chemical Physics* 1998; 230:253-65.

Corno AF *et al.* Myocardial and pulmonary effects of aqueous oxygen with acute hypoxia. *Ann Thorac Surg* 2004; 78:956-60.

Creech JL *et al.* Injection of highly supersaturated oxygen solutions without nucleation. *J Biomech Eng* 2002; 124:676-683.

Dixon SR *et al.* Initial experience with hyperoxemic reperfusion after primary angioplasty for acute myocardial infarction. *J Am Coll Cardiol* 2002; 39(3):387-92.

Glazier JJ. Attenuation of reperfusion microvascular ischemia by aqueous oxygen: Experimental and clinical observations. *Am Heart J* 2005; 149(4):580-4.

Granger CB *et al.* The search for myocardial protection: Is there still hope? *J Am Coll Cardiol* 2007; 50:406-408.

Johnson LL *et al.* Hyperbaric oxygen solution infused into the anterior interventricular vein at reperfusion reduces infarct size in swine. *Am J Physiol Heart Circ Physiol* 2004; 287:H2234-40.

O'Neill WW *et al.* Acute Myocardial Infarction with hyperoxemic Therapy (AMIHOT): A prospective, randomized multicenter trial of intracoronary hyperoxemic reperfusion after percutaneous coronary intervention. *J Am Coll Cardiol* 2007; 50:397-405.

¹Gibbons, RJ *et al.* Myocardium at risk and infarct size after thrombolytic therapy for acute myocardial infarction: implications for the design of randomized trials of acute intervention. *J Am Coll Cardiol* 1994; 24:616-23.

² Gibbons RJ *et al.* The quantification of infarct size. *J Am Coll Cardiol* 2004; 44:1533-1542.

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Spears JR *et al.* Aqueous oxygen attenuation of reperfusion microvascular ischemia in a canine model of myocardial infarction. *ASAIO J* 2003 49(6):716-20
Spears JR *et al.* Aqueous oxygen hyperbaric reperfusion in a porcine model of myocardial infarction. *J Invasive Cardiol* 2002; 14(4):160-66.
Spears JR *et al.* Aqueous oxygen near the homogeneous nucleation limit of water: stabilization with submicron capillaries. *ASAIO J* 2006; 52:186-91.

Spears JR *et al.* Aqueous Oxygen: A highly O₂-supersaturated infusate for regional correction of hypoxemia and production of hyperoxemia. *Circulation* 1997; 96(12):4385-91.

Stone GW. A prospective, randomized evaluation of supersaturated oxygen therapy after percutaneous coronary intervention in acute anterior myocardial infarction. *Presented at TCT 2007.*

Trabattoni *et al.* Hyperoxemic perfusion of the left anterior descending coronary artery after primary angioplasty in anterior ST-elevation myocardial infarction. *Catheter Cardiovasc Interv* 2006; 67:859-865.

Warda HM *et al.* Effect of intracoronary aqueous oxygen on left ventricular remodeling after anterior wall ST-elevation acute myocardial infarction. *Am J Cardiol* 2005; 96(1):22-24.

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