December 2014

Rapiscan (regadenoson) - New important advice to minimise the risk of cerebrovascular accident and prolongation of Rapiscan-induced seizures following administration of aminophylline

Dear Healthcare Professional,

Rapidscan Pharma Solutions, in agreement with the European Medicines Agency and the Medicines and Healthcare Products Regulatory Agency (MHRA), would like to inform you of important updated safety information regarding Rapiscan (regadenoson).

Summary:

Cerebrovascular accident

- **There have been reports of cerebrovascular accidents, some of which have been observed after clinically significant increases in blood pressure, severe hypotension or worsening atrial fibrillation that occurred following administration of regadenoson.**
- **Consider delaying the administration of regadenoson in patients with uncontrolled hypertension.**
- **Exercise caution in patients with a history of atrial fibrillation or those who are at risk of serious hypotension.**
- **Do not administer regadenoson to patients with severe hypotension.**

Prolongation of regadenoson -induced seizures following administration of aminophylline

- **There have been reports of regadenoson -induced seizures being prolonged after aminophylline administration.**
- **The use of aminophylline to terminate regadenoson -induced seizures is not recommended.**
- **Exercise caution when considering administering regadenoson to patients with a history of seizures or other risk factors e.g. concomitant drugs that lower seizure threshold.**

Further information on the safety concern and the recommendations:

Rapiscan is a selective coronary vasodilator for use as a pharmacological stress agent for radionucleotide myocardial perfusion imaging in adult patients unable to undergo adequate stress exercise test. It is intended for diagnostic use only. This letter has been sent to highlight important recent updates to the Rapiscan Summary of Product Characteristics (SPC).

Cerebrovascular accident (Stroke)

Clinically significant changes in blood pressure (both hyper- and hypotension) and worsening or recurrence of atrial fibrillation that have been associated with regadenoson administration are known to increase the risk of CVA. Based on a recent review of post-marketing reports of cases of CVA, it was concluded that regadenoson could cause CVA. Therefore, the Summary of Product Characteristics (SPC) has been updated to contain a warning about CVA as well as a warning about the risk of elevated blood pressure and hypertensive crisis, which has been implicated in some of the cases of haemorrhagic CVA. The use of regadenoson in patients with, or who are at risk of, hypotension or atrial fibrillation should be considered carefully, in accordance with the guidance in the SPC.

Prolongation of regadenoson -induced seizures following administration of aminophylline

Aminophylline can be administered to attenuate severe and/or persistent adverse reactions due to regadenoson. However, a recent review of cases of regadenoson-induced seizures indicated that the administration of aminophylline may have prolonged the seizure. This would be consistent with the known pro-convulsant effect of aminophylline. Therefore, aminophylline is not recommended to terminate seizures due to regadenoson. The Rapiscan SPC has been updated to contain this new recommendation and safety information.

Full prescribing and adverse event information for Rapiscan (regadenoson) can be found in the SPC available via http://www.medicines.org.uk/emc

Call for reporting

Please continue to report suspected adverse drug reactions to the MHRA through the Yellow Card Scheme. Please report

- all suspected ADRs that are serious or result in harm. (Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason.)
- all suspected ADRs associated with new drugs and vaccines identified by the black triangle ▼

It is easiest and quickest to report ADRs online via the Yellow Cards website: www.mhra.gov.uk/yellowcard.

Alternatively, prepaid Yellow Cards for reporting are available:

- by writing to FREEPOST YELLOW CARD (no other address details necessary)
- by emailing yellowcard@mhra.gsi.gov.uk
- at the back of the British National Formulary (BNF)
- by telephoning the Commission on Human Medicines (CHM) free phone line: 0800-731-6789
- or by downloading and printing a form from the Yellow Card section of the MHRA website

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates, and product brand name.

Adverse events should also be reported to Rapidscan Pharma by phone 080 0652 1391, fax 080 0471 5035, or emailing safety@rapiscan-mpi.com.

Company contact point

Should you have any questions or require additional information regarding the use of Rapiscan or have questions about the content of this letter, please contact the Rapidscan Pharma Solutions' Medical Information at medical.information@rapiscan-mpi.com.

Yours sincerely,

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Annex

The following text shows the recent updates to the Rapiscan SPC (new text underlined)

Section 4.2

[…]

Aminophylline may be used to attenuate severe and/or persistent adverse reactions to Rapiscan but should not be used solely for the purpose of terminating a seizure induced by Rapiscan (see section 4.4).

Section 4.4 of the SPC as follows:

[…]

Aminophylline may be administered in doses ranging from 50 mg to 250 mg by slow intravenous injection (50 mg to 100 mg over 30-60 seconds) to attenuate severe and/or persistent adverse reactions to Rapiscan but should not be used solely for the purpose of terminating a seizure induced by Rapiscan.

Elevated blood pressure

Rapiscan may cause clinically significant increases in blood pressure, which in some patients can lead to hypertensive crisis (see section 4.8). The risk of significant increases in blood pressure may be higher in patients with uncontrolled hypertension. Consideration should be given to delaying Rapiscan administration until blood pressure is well controlled.

Transient ischaemic attacks and cerebrovascular accident

Rapiscan can cause transient ischaemic attack (see section 4.8). In post-marketing experience there have also been reports of cerebrovascular accident (CVA).

Risk of seizure

Caution should be used when administering Rapiscan to patients with a history of seizures or other risk factors for seizures, including the concomitant administration of medicinal products that lower seizure threshold (e.g. antipsychotics, antidepressants, theophyllines, tramadol, systemic steroids and quinolones).

Aminophylline may prolong a seizure or cause multiple seizures because of its proconvulsant effect. Therefore administration of aminophylline solely for the purpose of terminating a seizure induced by Rapiscan is not recommended.

Section 4.8 of the SPC, as follows:

Summary of safety profile:

Rapiscan may cause myocardial ischaemia (potentially associated with fatal cardiac arrest, life threatening ventricular arrhythmias, and myocardial infarction), hypotension leading to syncope and transient ischaemic attacks, elevated blood pressure leading to hypertension and hypertensive crises, and SA/AV node block leading to first, second or third degree AV block, or sinus bradycardia requiring intervention (see section 4.4). Signs of hypersensitivity (rash, urticaria, angioedema, anaphylaxis and/or throat tightness) may be immediate or delayed onset. Aminophylline may be used to attenuate severe or persistent adverse reactions to Rapiscan but should not be used solely for the purpose of terminating a seizure induced by Rapiscan (see section 4.4).

Tabulated list of adverse reactions:

The adverse reaction “cerebrovascular accident” has been added with a frequency category “rare”.

Description of selected adverse reactions:

In clinical trials, increased systolic blood pressure (≥ 50 mm Hg) was observed in 0.7% of patients and increased diastolic blood pressure (≥ 30 mm Hg) in 0.5% of patients. Most increases resolved within 10 to 15 minutes, but in some cases, increases were observed at 45 minutes following administration.