



Canadian Adverse Reaction Newsletter

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Scope

This quarterly publication alerts health professionals to potential signals detected through the review of case reports submitted to Health Canada. It is a useful mechanism to stimulate adverse reaction reporting as well as to disseminate information on suspected adverse reactions to health products occurring in humans before comprehensive risk-benefit evaluations and regulatory decisions are undertaken. The continuous evaluation of health product safety profiles depends on the quality of your reports.

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Vascular endothelial growth factor receptor inhibitors and thrombotic microangiopathy

Key points

- Scientific literature suggests a potential association between vascular endothelial growth factor (VEGF) receptor inhibition and thrombotic microangiopathy (TMA).
- In certain cases, clinical manifestations of TMA resolved or improved upon treatment discontinuation.
- Health care professionals are reminded that strict monitoring and early recognition of signs and symptoms of TMA are important when treating patients with anti-VEGF agents.

Vascular endothelial growth factor (VEGF) and its receptors play a central role in tumour angiogenesis.¹ Blockade of this pathway is considered to be a therapeutic strategy to inhibit tumour growth. Anti-VEGF agents block the VEGF pathway by generally one of 2 mechanisms—by preventing the interaction of VEGF with its receptor (i.e., VEGF antagonists, which include anti-VEGF monoclonal antibodies such as bevacizumab) or by targeting surface receptor function (i.e., VEGF receptor inhibitors, the focus of this article).

Six marketed VEGF receptor inhibitors are available in Canada (Table 1). The risk of thrombotic microangiopathy (TMA) is currently labelled in the Post-Marketing Experience section of the sunitinib (Sutent) Canadian product monograph (CPM) and in the Warnings and Precautions, Adverse Reactions and Post-Market Adverse Drug Reactions sections of the pazopanib (Votrient) CPM.^{2,3}

TMA is a group of disorders characterized by occlusive microvascular thrombosis, thrombocytopenia and end-organ damage.⁴ Two main subtypes of TMA are thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS). Clinical symptoms of TTP typically include thrombocytopenia, microangiopathic hemolytic anemia (MAHA), neurological abnormalities, renal failure and fever. HUS can present with similar signs and symptoms, however HUS is usually diagnosed in cases in which renal failure is the most prominent sign. A diagnosis of TTP is generally designated for cases in which neurologic abnormalities such as seizure and vision loss predominate.

Table 1: List of vascular endothelial growth factor (VEGF) receptor inhibitors marketed in Canada

VEGF receptor inhibitor (Trade name)	Date of initial marketing
Sunitinib (Sutent)	2006
Sorafenib (Nexavar)	2006
Pazopanib (Votrient)	2010
Vandetanib (Caprelsa)	2012
Axitinib (Inlyta)	2012
Regorafenib (Stivarga)	2013

Several cases of TMA involving sunitinib have been published in the literature.⁵⁻¹⁰ In some of these cases, clinical manifestations of TMA resolved or improved upon discontinuation of sunitinib (along with management therapy).^{5,6,8,10} In one case, renal function remained normal, and laboratory investigations did not indicate any signs of TMA, however a renal biopsy later revealed features typical of TMA.⁷ This case highlights the possible discrepancy between mild clinical manifestations and severe TMA features on renal biopsy. Although most cases of anti-VEGF agent-induced TMA appear to be localized to the kidneys, systemic organ dysfunction can occur.¹¹ For example, 5 cases of systemic TMA involving MAHA were reported in patients receiving a combination of sunitinib and bevacizumab.¹²

While VEGF receptor inhibitors are suspected of being associated with TMA, the exact mechanism of this association is unclear. A compromised renal endothelium is the proposed mechanism underlying TMA-related adverse reactions.¹³ This association does not exclude the possibility of other contributing factors or pathways.^{7,8}

Although not the focus of the current article, published cases of TMA or suspected TMA have also been reported with VEGF antagonists.^{13,14} Considering that TMA has been observed with the use of multiple anti-VEGF agents, it has been suggested that this risk may represent a class effect.^{4,7}

As of June 30, 2013, Health Canada has not received any reports of TMA such as TTP or HUS suspected of being associated with any of the 6 VEGF receptor inhibitors marketed in Canada.

Health care professionals are reminded that this adverse reaction may be underdiagnosed and underreported. Management of TMA should focus on strict monitoring and early recognition of signs and symptoms in patients treated with anti-VEGF agents.⁴ Health care professionals are encouraged to report to Health Canada any cases of TMA such as TTP or HUS suspected of being associated with anti-VEGF agents.

Rania Mouchantaf, PhD, Health Canada

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Incidents involving the combined use of Durepair Dura Regeneration Matrix with ancillary wound closure products

Key points

- There is some evidence to suggest a possible increased risk of complications when ancillary wound closure products are used in combination with collagen duraplasty grafts, including Durepair.
- As of October 15, 2013, Health Canada received 5 reports of incidents suspected of involving Durepair. In some of these cases, it was reported that Durepair was implanted in conjunction with Tisseel fibrin sealant.
- Physicians are encouraged to consult the product labelling of ancillary products when considering their concomitant use with Durepair.

Durepair Dura Regeneration Matrix is a collagen implant used to repair dura mater defects during neurosurgery. It is a dural graft substitute derived from fetal bovine dermis.¹ During implantation, Durepair may either be sutured into place or applied as an onlay graft.² The porous structure of Durepair allows for fibroblast infiltration and vascularization of the implant, and eventual remodelling of the site with native collagen.¹

As of October 15, 2013, Health Canada received 5 reports of medical device incidents suspected of involving Durepair. In one incident, it was reported that a Durepair graft implanted in a patient in conjunction with Tisseel fibrin sealant was later removed and had a texture similar to toothpaste. The other 4 cases described patients developing chemical (or aseptic) meningitis after implantation with Durepair. In one of these 4 cases, the Durepair was implanted in

conjunction with Tisseel fibrin sealant and revision surgery was required. In the other 3 of these 4 cases, it was unknown whether ancillary wound closure products (e.g., sealants, hemostatics) were used in conjunction with Durepair. The Tisseel product monograph states that its safety and effectiveness in neurosurgical procedures has not been evaluated.³

Known complications associated with the use of dural grafts are often hydrodynamic in nature, and include cerebrospinal fluid (CSF) leakage, pseudomeningocele, chemical (or aseptic) meningitis, and delayed hydrocephalus.⁴ However, nonrandomized studies have shown results suggesting a possible increased risk of complications when ancillary wound closure products are used in combination with collagen duraplasty grafts,^{5,6} including Durepair.⁷ One study found that 5 out of 9 patients receiving Durepair in combination with DuraSeal dural sealant (a polyethylene glycol hydrogel) experienced hydrodynamic complications and that 3 out of 9 patients required reoperation. All 5 complications presented 16 days after surgery or later and the authors suggested that the use of ancillary sealant may have inhibited cell migration in the area of the graft, hence delaying postsurgical inflammation and healing.⁷

Other researchers have also postulated that the use of ancillary sealants may reduce the efficacy of a collagen dural graft over time, possibly by impairing conductivity, leading to graft decay without native tissue repair.⁶ However, increases in complications may be related to the tendency to use multiple products in cases with higher perceived risk of CSF leak (or other

hydrodynamic complications) at the outset.⁶ There are no published randomized clinical trials specifically investigating this issue. However, the Durepair Instructions for Use state “Animal study results suggest that the foreign body response associated with the use of sealants and hemostatic agents in conjunction with Durepair may be more pronounced than use of Durepair alone. This response may increase the incident rates of known risks of dura substitutes”.² Physicians are encouraged to consult the product labelling of ancillary products when considering their concomitant use with Durepair.

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Quarterly summary of health professional and consumer advisories

(posted between August 19, 2013 and November 21, 2013)

Date*	Product	Subject
Nov 20	Phosphate injectable products	Potential for particulate matter in some vials
Nov 19 & several earlier dates†	"Poppers" (products containing alkyl nitrites)	Updated list of retail locations selling "poppers"
Nov 15	OxyElite Pro weight loss products	Reports of serious liver injury
Nov 14	Gadolinium-based contrast agents	Update on nephrogenic systemic fibrosis / nephrogenic fibrosing dermopathy
Nov 14	Risperidone- or paliperidone-containing products	Risk of intraoperative floppy iris syndrome (IFIS)
Nov 6	Vega One Nutritional Shakes and Sports Performance Drinks	Recall: possible contamination with chloramphenicol
Nov 1	Vega One Vanilla Chai and Vega Sport Performance Chocolate	Contamination with chloramphenicol
Nov 1	Imitrex (sumatriptan succinate) Injection	Recall: needle may no longer be sterile
Oct 24	Bodico Hand Sanitizer	Found to contain undeclared methanol (associated with two deaths)
Oct 23	Dextran 40 in Dextrose injection and Dextran 40 in Sodium Chloride injection	Potential for crystallization
Oct 18	A number of natural health products	Recall: possible contamination with chloramphenicol
Oct 18	Natural health products sold by Lion King Health Enterprises Group Ltd.	Seized products found to contain hidden ingredients and unauthorized substances similar to sildenafil
Oct 17	Kamizym-U and Kamizym+	Recall: possible contamination with chloramphenicol
Oct 17	Acetylsalicylic Acid (ASA) products	Updated labelling standard
Oct 17 & several earlier dates†	Vita Health over-the-counter products	Labelling errors: updated list of recalled products
Oct 15	Sensipar (cinacalcet)	New warnings: risk of abnormal heart rhythm associated with low blood calcium
Oct 11	Nitroglycerin 100 mg in 5% Dextrose Solution	Recall: particulate matter found in solution
Oct 11	Spectrazyme	Recall: possible contamination with chloramphenicol

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- Those published prior to April 2011 have been marked as archived as part of the Government of Canada Web Standards initiative.
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Quarterly summary of health professional and consumer advisories

(posted between August 19, 2013 and November 21, 2013)

Date*	Product	Subject
Oct 11	Fentanyl patches	Reminder about safe use and disposal to prevent accidental exposure
Oct 10	Flora Essentials	Recall: possible contamination with chloramphenicol
Oct 9	Kadcyla (trastuzumab emtansine) and Herceptin (trastuzumab)	Risk of medication error due to similarity in the non-proprietary names
Sept 26	Designer drugs	Reminder that these drugs are dangerous and illegal
Sept 26	Badger Baby and Badger Kids SPF 30 Sunscreen Lotion	Recall: microbial contamination
Sept 6	Sutent (sunitinib malate)	Cases of severe skin reactions
Sept 6	Vita Health over-the-counter products	Recall: labelling errors
Sept 5	Esme-28 (levonorgestrel and ethinyl estradiol)	Recall: possibility of a placebo pill being in place of an active pill
Sept 3	BiCNU (carmustine for injection U.S.P.) lyophilized powder	Shortage of Canadian-labelled BiCNU; replacement with U.S. labelled stock
Aug 30	Life, Exact, Rexall and Tanta Extra Strength Allergy Sinus Medication	Recall: labelling error
Aug 29	282 MEP (meprobamate-containing medicine)	Market withdrawal
Aug 27	Freya-28 (desogestrel and ethinyl estradiol)	Recall: placebo pill was found in place of an active pill
Aug 23	Prema G	Contains an undeclared ingredient (hydroxyhomosildenafil thione)
Aug 23	OM Fusion Distributors LLC products	Unauthorized health products
Aug 23	Personnelle Cold and Flu-in-One Extra Strength and Personnelle Flu Relief	Recall: labelling error
Aug 20	Zelboraf (vemurafenib)	Risk of progression of certain types of cancer and risk of serious rash
August 19 to November 21	Foreign products	9 Foreign Product Alerts (FPAs) were posted during this period

Advisories are available at www.health.gc.ca/medeffect.

*Date of issuance. This date may differ from the posting date.

†Update to a previous advisory.

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