Product Monograph

Including Patient Medication Information

AMBELVIST®

gadoquatrane injection

Solution

For intravenous use

257.9 mg/mL (0.1 mmol/mL) of gadoquatrane

Contrast Enhancement Agent for Magnetic Resonance Imaging (MRI)

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Date of Authorization:
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Recent Major Label Changes

Not applicable

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Table of Contents

Part 1: Healthcare Professional Information

1 Indications

AMBELVIST (gadoquatrane injection) is a medicinal product for diagnostic use only.

AMBELVIST (gadoquatrane injection) is indicated in adults and children of all ages including term neonates for contrast enhancement in magnetic resonance imaging (MRI) to detect and visualize known or suspected pathology in:

- the central nervous system (brain, spine and associated tissues), and,
- the body (head and neck, thorax including breast, abdomen, pelvis, and extremities).

1.1 Pediatrics

Pediatrics (< 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of AMBELVIST in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use (See 1 Indications, 14.1 Clinical Trials by Indication, 7.1.3 Pediatrics and 10.3 Special Populations and Conditions - Pediatrics (<18 years of age)).

1.2 Geriatrics

Geriatrics (≥ 65 years of age): No differences in safety and effectiveness were observed between elderly and younger patients. (See 7.1.4 Geriatrics and 10.3 Special populations and conditions - Geriatrics).

2 Contraindications

AMBELVIST is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, See 6 Dosage Forms, Strengths, Composition, and Packaging. (See 7 Warnings and Precautions - Immune-Hypersensitivity).

3 Serious Warnings and Precautions Box

Nephrogenic Systemic Fibrosis (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF in patients with:

- chronic severe renal insufficiency (glomerular filtration rate <30 mL/min/1.73m^2), or
- acute renal failure / acute kidney injury

In these patients, avoid use of GBCAs unless the diagnostic information is essential and not available with non-contrast-enhanced magnetic resonance imaging (MRI). NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle, and internal organs.

Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. When administering a GBCA, do not exceed the recommended dose (See 4.2 Recommended Dose and Dosage Adjustment) and allow a sufficient period of time for elimination of the agent from the body prior to any re-administration. (See 7 Warnings and Precautions - General, Renal and Skin.)

Not For Intrathecal Use

Intrathecal administration of GBCAs can cause serious, life-threatening, and fatal reactions. AMBELVIST is not approved for intrathecal use (See 7 Warnings and Precautions - Risks of Intrathecal Use).

4 Dosage and Administration

4.1 Dosing Considerations

- **AMBELVIST is for intravenous administration use only**.
- For instructions on the medicinal product before administration, see section 4.4 Administration.

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of AMBELVIST for adults and pediatric patients (including neonates) is 0.1 mL/kg body weight. This is equivalent to 0.01 mmol gadoquatrane per kg body weight or 0.04 mmol gadolinium (Gd) per kg body weight.

Table 1: Dosing regimen

Administered volume of AMBELVIST	Dose gadoquatrane	Dose gadolinium
0.1 mL per kg body weight	0.01 mmol per kg body weight	0.04 mmol per kg body weight

The dose should be calculated based on the patient's body weight and should not exceed the recommended dose per kilogram of body weight detailed in this section.

Table 2: Administered volume of AMBELVIST per kg body weight*

Body weight (kg)	Administered volume of AMBELVIST (mL)
2.5	0.25
5	0.5
10	1
20	2
30	3
40	4
50	5
60	6
70	7
80	8
90	9
100	10

*Body weights listed in the table above are illustrative only and do not imply an upper body-weight limit; administer AMBELVIST according to 0.1 mL per kg body weight.

Special Populations:

Pediatric population

No dose adjustment is required for pediatric patients (including neonates) (See 1.1 Pediatrics, 7.1.3 Pediatrics and 10.3 Special populations and conditions - Pediatrics).

Geriatrics

No dose adjustment is required for elderly patients (See 1.2 Geriatrics, 7.1.4 Geriatrics and 10.3 Special populations and conditions - Geriatrics). Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function.

Hepatic impairment

Because gadoquatrane is exclusively eliminated in an unchanged form via the kidneys, no dose adjustment is considered necessary in patients with hepatic impairment (See 10.3 Special populations and conditions - Hepatic Insufficiency).

Renal impairment

No dose adjustment is required for patients with any degree of renal impairment. In patients with renal impairment, the exposure of gadoquatrane is increased compared to patients with normal renal

function. This may increase the risk of adverse reactions. Patients with severe renal impairment have increased risk of NSF. Avoid use of AMBELVIST in these patients unless the diagnostic information is essential and not available with non-contrast MRI or other modalities. See 7. Warnings and Precautions - Renal and 10.3 Special populations and conditions - Renal Insufficiency.

No study was conducted in patients with severe renal impairment or those with dialysis or end stage renal disease. **Do not exceed the recommended dose**. **Repeat dose should be avoided in these patient populations.** AMBELVIST can be removed from the body by hemodialysis.

4.4 Administration

Administer AMBELVIST as an intravenous injection, manually or by compatible power injector, at a flow rate of approximately 1 mL/second to 4 mL/second, followed by a flush of 0.9% sodium chloride injection. For pediatric patients, adjust the flow rate and flush volume based on age.

Visually inspect AMBELVIST prior to administration. Do not use the solution if it is discolored, if particulate matter is present, or if the container appears damaged.

Do not mix AMBELVIST with other medications because of the potential for chemical incompatibility.

When AMBELVIST pharmacy bulk packs supplied in vial/bottle (15 mL, 30 mL or 65 mL) or single-dose vials (2 mL, 7.5 mL or 10 mL) are used with an automated injection system, always follow the injection system manufacturer's instructions for use.

Contrast MRI can begin immediately following the injection of AMBELVIST.

Single-Dose Vials:

AMBELVIST single-dose vial of a sterile preparation is for parenteral use only with an approved medical device for filling empty sterile syringes or for use with an automated contrast injection system. AMBELVIST single-dose vial is for intravenous use only.

Draw AMBELVIST into the syringe immediately before use. The transfer of AMBELVIST from the single-dose vial must be performed in an aseptic work area, using aseptic techniques. The contents of the single-dose vial after initial puncture should be used within 24 hours. Once the single-dose vial stopper is punctured, AMBELVIST remains stable for 24 hours at 20°C to 25°C. Any unused portion must be discarded 24 hours after initial puncture. Do not pierce the rubber stopper more than once.

Pharmacy Bulk Packs:

AMBELVIST pharmacy bulk package is a vial/bottle of a sterile preparation for parenteral use that contains many single doses, for use only with an approved medical device for filling empty sterile syringes or for use with an automated contrast injection system. AMBELVIST pharmacy bulk package is for intravenous use and not for direct infusion.

Draw AMBELVIST into the syringe immediately before use. The transfer of AMBELVIST from the pharmacy bulk package must be performed in an aseptic work area, using aseptic techniques. The contents of the pharmacy bulk package after initial puncture should be used within 24 hours. Once the pharmacy bulk package vial/bottle stopper is punctured, AMBELVIST remains stable for 24 hours at 20°C to 25°C. Any unused portion must be discarded 24 hours after initial puncture. Do not pierce the rubber stopper more than once.

4.5 Missed Dose

Not applicable.

5 Overdose

The maximum tested dose of gadoquatrane in humans (0.05 mmol/kg, containing 0.2 mmol gadolinium/kg body weight, i.e., 5 times the recommended dose), was well tolerated.

Gadoquatrane can be removed by hemodialysis. Based on in vitro dialysis study gadoquatrane has been shown to be dialyzable. However, it is unknown if hemodialysis prevents NSF (See 7 Warnings and Precautions - Renal and 10.3 Special populations and conditions - Renal Insufficiency).

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 Dosage Forms, Strengths, Composition, and Packaging

Table 3: Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-Medicinal Ingredients
intravenous	Solution / 257.9 mg/mL (0.1 mmol/mL) gadoquatrane	calcobutrol, hydrochloric acid, sodium chloride, trometamol and water for injection

AMBELVIST is a clear, colourless to pale yellow solution. Each mL of AMBELVIST contains 257.9 mg of gadoquatrane and 1.235 mg sodium (0.0005 mmol).

Single dose of AMBELVIST, each in volume of 2 mL and 10 mL, is supplied in 2 mL and 10 mL colourless type I glass vials, respectively, closed with bromobutyl gray rubber stopper and aluminium seal with polypropylene cap.

Pharmacy bulk pack of AMBELVIST, each in volume of 7.5 mL, 15 mL and 30 mL, is supplied in 10 mL, 15 mL and 30 mL colourless type I glass vials, respectively, closed with bromobutyl gray rubber stopper and aluminium seal with polypropylene cap.

Pharmacy bulk pack of AMBELVIST in volume of 65 mL is supplied in 100 mL colourless type II glass bottle closed with bromobutyl gray rubber stopper and aluminium seal with polypropylene cap.

7 Warnings and Precautions

See 3 Serious Warnings and Precautions Box.

General

MRI procedures which involve the use of gadoquatrane should be carried out by healthcare practitioners who have the prerequisite training and a thorough knowledge of the particular procedure to be performed.

Accumulation of Gadolinium in the Brain

The current evidence suggests that gadolinium may accumulate in the brain after multiple administrations of GBCAs. Increased signal intensity on non-contrast T1-weighted images of the brain has been observed after multiple administrations of GBCAs in patients with normal renal function. Gadolinium has been detected in brain tissue after multiple exposures to GBCAs, particularly in the

dentate nucleus and globus pallidus. The evidence suggests that the risk of gadolinium accumulation is higher after repeat administration of linear agents than after repeat administration of macrocyclic agents. AMBELVIST is a macrocyclic GBCA.

The clinical significance of gadolinium accumulation in the brain is presently unknown; however, gadolinium accumulation may potentially interfere with the interpretation of MRI scans in the brain. In order to minimize potential risks associated with gadolinium accumulation in the brain, it is recommended to use the lowest effective dose and perform a careful benefit risk assessment before administering repeated doses.

Extravasation

Caution during administration is necessary to avoid any extravasation. In case of extravasation, the injection should be stopped immediately. In case of local reactions, evaluation and treatment should be carried out as necessary.

Risks of intrathecal use

AMBELVIST must not be used intrathecally. Serious, life-threatening and fatal cases, primarily with neurological reactions (e.g., coma, encephalopathy, seizures), have been reported with intrathecal use of other GBCAs (See 3 Serious Warnings and Precautions Box and 4.1 Dosing Considerations).

Driving and Operating Machinery

AMBELVIST has no influence on the ability to drive and use machines.

Immune

Hypersensitivity

As with other contrast media, gadoquatrane can be associated with anaphylactoid/hypersensitivity or other idiosyncratic reactions, characterized by cardiovascular, respiratory or cutaneous manifestations, and ranging to severe reactions including shock.

Most of these reactions occur within 30 minutes of administration.

As with other contrast media, delayed reactions occurring hours or days after administration have been observed, though rarely.

Therefore, post-procedure observation of the patient is recommended for at least 30 minutes after the administration of gadoquatrane. (See 8.3 Less Common Clinical Trial Adverse Reactions).

- Before AMBELVIST administration, assess all patients for any history of a reaction to contrast media, bronchial asthma and/or allergic disorders. These patients may have an increased risk for a hypersensitivity reaction to AMBELVIST.
- During and following AMBELVIST administration, it is recommended to observe patients for signs and symptoms of hypersensitivity reactions.
- Administer AMBELVIST only in-facilities where trained personnel and therapies are promptly available for the treatment of hypersensitivity reactions, including personnel trained in resuscitation. AMBELVIST is contraindicated in patients with history of hypersensitivity reactions to GBCAs (See 2 Contraindications).

Neurologic

Convulsive States

While there is no evidence suggesting that gadoquatrane directly precipitates convulsion, the possibility that GBCAs may decrease the convulsive threshold in susceptible patients cannot be ruled out. Precautionary measures should be taken with patients predisposed to seizure, e.g., close monitoring and availability of injectable anticonvulsants.

Renal

Prior to administration of AMBELVIST, screen all patients for renal dysfunction by obtaining a history and/or laboratory tests.

Because AMBELVIST is renally excreted, sufficient period of time for elimination of the contrast agent from the body prior to any re-administration in patients with renal impairment should be ensured. In patients with mild and moderate renal impairment, on average 90% or more of the administered AMBELVIST were recovered in urine within 24h. (See 10.3 Special populations and conditions - Renal Insufficiency).

No study was conducted with AMBELVIST in patients with severe renal impairment or those undergoing dialysis or those with end stage renal impairment. In patients with severely impaired renal function, the benefits must outweigh the risks, since contrast medium elimination is delayed in such cases.

Based on in vitro dialysis study, gadoquatrane has been shown to be dialyzable.

Acute Kidney Injury

In patients with chronically reduced renal function, acute kidney injury requiring dialysis has occurred with the use of GBCAs. The risk of acute kidney injury may increase with increasing dose of the contrast agent. Do not exceed the recommended dose.

Skin

NSF was first identified in 1997 and has, so far, been observed only in patients with renal disease. This is a systemic disorder with the most prominent and visible effects on the skin. Cutaneous lesions associated with this disorder are caused by excessive fibrosis and are usually symmetrically distributed on the limbs and trunk. Involved skin becomes thickened, which may inhibit flexion and extension of joints and result in severe contractures. The fibrosis associated with NSF can extend beyond dermis and involve subcutaneous tissues, striated muscles, diaphragm, pleura, pericardium, and myocardium. NSF may be fatal.

Nephrogenic Systemic Fibrosis (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for Nephrogenic Systemic Fibrosis (NSF) in patients with chronic severe renal insufficiency (glomerular filtration rate <30 mL/min/1.73m^2), and in patients with acute renal failure / acute kidney injury. In these patients, avoid use of GBCAs unless the diagnostic information is essential and not available with noncontrast-enhanced magnetic resonance imaging (MRI). For patients receiving hemodialysis, healthcare professionals may consider prompt hemodialysis following GBCA administration in order to enhance the contrast agent's elimination. However, it is unknown if hemodialysis prevents NSF.

Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a GBCA and the degree of renal function impairment at the time of exposure.

NSF development is considered a potential class-related effect of all GBCAs.

Postmarketing reports have identified the development of NSF following single and multiple administrations of GBCAs. These reports have not always identified a specific agent. Where a specific agent was identified, the most commonly reported agent was gadodiamide (OMNISCAN®), followed by gadopentetate dimeglumine (MAGNEVIST®) and gadoversetamide (OPTIMARK®). NSF has also developed following the sequential administration of gadodiamide with gadobenate dimeglumine (MULTIHANCE®) or gadoteridol (PROHANCE®). The number of postmarketing reports is subject to change over time and may not reflect the true proportion of cases associated with any specific GBCA.

The extent of risk for NSF following exposure to any specific GBCA is unknown and may vary among the agents. Published reports are limited and predominantly estimate NSF risks with gadodiamide. In one retrospective study of 370 patients with severe renal insufficiency who received gadodiamide, the estimated risk for development of NSF was 4%. The risk, if any, for the development of NSF among patients with mild to moderate renal insufficiency or normal renal function is unknown, and the cautious utilization of the lowest possible dose of GBCA is preferable. (See 10.3 Pharmacokinetics – Elimination and 4.2 Recommended Dose and Dosage Adjustment – Renal Impairment).

Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. When administering a GBCA, do not exceed the recommended dose and allow a sufficient period of time for elimination of the agent from the body prior to any readministration.

A skin biopsy is necessary in order to exclude the diagnosis of similarly presenting skin disorders (eg, scleromyxedema). See 3 Serious Warnings and Precautions Box, 7 Warnings and Precautions - General, Renal and Skin and 8.5 Post-market adverse reactions.

There have been reports of NSF associated with use of some GBCAs in patients with acute or chronic severe renal impairment (GFR < 30ml/min/1.73m^2). Patients undergoing liver transplantation are at particular risk since the incidence of acute renal failure is high in this group. As there is a possibility that NSF may occur with AMBELVIST, it should therefore only be used in patients with severe renal impairment and in patients in the perioperative liver transplantation period after careful benefit/risk assessment and if the diagnostic information is essential and not available with non-contrast enhanced MRI.

No cases of NSF associated with gadoquatrane have been identified in clinical trials. See 3 Serious Warnings and Precautions Box and 10.3 Special populations and conditions - Hepatic Insufficiency.

Based on in vitro dialysis study gadoquatrane has been shown to be dialyzable. It is unknown if hemodialysis prevents NSF.

7.1 Special Populations

7.1.1 Pregnancy

There are no data from the use of gadoquatrane in pregnant women.

Traces of GBCAs can cross the placenta barrier and result in fetal exposure and may be detected in organs and tissues for an extended period of time. In animal reproduction studies, there were no adverse developmental effects observed in rats or rabbits with intravenous administration of gadoquatrane during organogenesis. See 16 Non-Clinical Toxicology - Reproductive and developmental toxicology).

The potential risks of an abnormal pregnancy outcome are unknown, as adequate and well controlled clinical studies with AMBELVIST were not conducted in pregnant women. A retrospective cohort study, comparing pregnant women who had a GBCA MRI to pregnant women who did not have an MRI,

reported a higher occurrence of stillbirths and neonatal deaths in the group receiving GBCA MRI. However, no increased risk of congenital anomalies was observed. Limitations of this study include a lack of comparison with non-contrast MRI, lack of information about the maternal indication for MRI, and the type of GBCA used. These limitations were further addressed in another retrospective cohort study that found no increased risk for fetal or neonatal death or Neonatal Intensive Care Unit (NICU) admission when comparing pregnancies exposed to GBCA MRI and non-contrast MRI.

AMBELVIST should not be used during pregnancy unless the clinical condition of the patient requires use of gadoquatrane.

7.1.2 Breastfeeding

It is unknown whether gadoquatrane is excreted in human breast milk.

Data in animals show that gadoquatrane was found in milk at lower concentrations than in plasma. Published lactation data on other GBCAs indicate that 0.01% to 0.04% of the maternal gadolinium dose is excreted in breast milk.

Continuing or discontinuing breast feeding for a period of 24 hours after administration of AMBELVIST, should be at the discretion of the healthcare practitioner and breastfeeding patient. 16 Non-Clinical Toxicology - Reproductive and developmental toxicology.

7.1.3 Pediatrics

No differences in pharmacokinetics, safety, and effectiveness were observed between adult and pediatric patients (See 10.3 Pharmacokinetics - Pediatrics , 14 Clinical Trials - QUANTI Pediatric and 16 Non-Clinical Toxicology – Juvenile Toxicity).

7.1.4 Geriatrics

No differences in safety and effectiveness were observed between elderly (aged 65 years and above) and younger patients 10.3 Pharmacokinetics - Geriatrics. AMBELVIST is known to be predominantly excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it is advisable to monitor renal function in these patients. No age-related dosage adjustment is necessary.

8 Adverse Reactions

8.1 Adverse Reaction Overview

The overall safety profile of AMBELVIST is based on pooled data from 842 patients in clinical trials including controlled phase II and III data with 749 adult and 93 pediatric patients.

The most serious adverse drug reaction in patients receiving AMBELVIST was hypersensitivity. Most of the undesirable effects and adverse drug reactions reported with AMBELVIST were of mild to moderate intensity, and transient in nature.

The most frequently reported drug-related adverse reactions in clinical trials (≥ 1%) in patients receiving AMBELVIST were dizziness (1.7%), headache (2.0%) and injection site reactions (2.7%).

The safety profile of AMBELVIST, including treatment emergent adverse events, vital signs, and laboratory values, was similar to the comparator macrocyclic GBCAs.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

AMBELVIST was studied for use in contrast enhanced MRI (CE-MRI) in one Phase II Study#20241 (Dose-Finding), two adult pivotal phase III studies, Study#21181 (QUANTI CNS) in patients undergoing CE-MRI of CNS and Study#21197 (QUANTI OBR) in patients undergoing CE-MRI of other body regions, and one pediatric pivotal phase I/III Study#21196 (QUANTI Pediatric). Of the total 842 patients investigated, 749 adult patients and 93 pediatric patients received AMBELVIST (756 adult patients received standard of care macrocyclic GBCAs (gadobutrol, gadoterate, gadoteridol) as comparators).

The data described below reflect AMBELVIST exposure in 842 patients (749 adult and 93 pediatric) who received the recommended dose of 0.01 mmol/kg body weight (0.04 mmol gadolinium/kg body weight). Among patients who received the recommended dose, the average age was 51 years (range 1 month to 89 years).

Table 4: Adverse drug reactions reported in clinical trials in ≥ 1% of patients treated with AMBELVIST

System organ class	Adverse Drug Reactions N = 842 (%)
Nervous system disorders	
Dizziness	1.7
Headache	2.0
General disorders and administration site conditions	
Injection site reaction[*,‡]	2.7

[*] Injection site reactions included injection site bruising, injection site coldness, injection site erythema, injection site hematoma, injection site pain, injection site swelling.

[‡] Most of the injection site reactions reported were related to the procedure.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

The pharmacokinetics and safety of AMBELVIST were evaluated in one Phase I/III study. Safety data is available in 93 subjects 0 - 17 years of age. No relevant differences for safety were observed for pediatric patients compared to the adult studies. No relevant difference across pediatric age groups were observed.

Adverse events were reported in 16 subjects (17.2%), the maximum intensity was mild in 11 subjects (11.8%), moderate in 4 subjects (4.3%), and severe in 1 subject (1.1%). This was a central cyanosis and a sudden blood oxygen desaturation of 65% observed in a 4-week (28 days) old, term-born patient, which was reported as hypersensitivity and assessed as life-threatening. It resolved within 11 minutes after increasing the inhaled oxygen flow rate.

Of the 16 subjects, 4 subjects (4.3 %) experienced adverse reactions considered as drug-related, all occurring in one subject each (pyrexia, hypersensitivity, erythema, rash).

8.3 Less Common Clinical Trial Adverse Reactions

The most frequently reported adverse reactions with a frequency of less than 1% following administration of AMBELVIST were: nausea, vomiting, feeling hot. These reactions were mild to moderate in severity.

The following other adverse reactions were reported:

Ear and labyrinth disorders:	vertigo
Gastrointestinal disorders:	abdominal discomfort
General disorders and administration site conditions:	feeling cold, pyrexia
Hepatobiliary disorders:	hyperbilirubinemia
Immune system disorders:	hypersensitivity[1]
Investigations:	glomerular filtration rate decreased
Musculoskeletal and connective tissue disorders:	arthralgia, limb discomfort
Nervous system disorders:	paraesthesia
Renal and urinary disorders:	hematuria
Respiratory, thoracic and mediastinal disorders:	dyspnoea, rhinalgia
Skin and subcutaneous tissue disorders:	erythema, pruritus, rash, urticaria

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

In all studies, the evaluation of the laboratory parameters and vital signs did not result in any safety signals for gadoquatrane compared to the standard of care macrocyclic GBCAs. One each of the following abnormal laboratory values and abnormal vital signs were reported as adverse events related to gadoquatrane: hyperbilirubinemia, glomerular filtration rate decreased, platelet count decreased, urinary sediment present, white blood cells urine positive, hematuria, pyrexia and dyspnoea. Electrocardiogram testing was performed in the Phase 2 study with no relevant abnormal finding (in line with Phase 1 studies).

8.5 Post-market adverse reactions

Nephrogenic Systemic Fibrosis (NSF)

Post-marketing reports have identified the development of NSF following single and multiple administrations of GBCAs. These reports have not always identified a specific agent. Where a specific agent was identified, the most commonly reported agent was gadodiamide (Omniscan®), followed by gadopentetate dimeglumine (Magnevist®) and gadoversetamide (OptiMARK®). The number of post-marketing reports is subject to change over time and may not reflect the true proportion of cases associated with any specific GBCA. The extent of risk for NSF following exposure to any specific GBCA is unknown and may vary among the agents. Published reports are limited and predominantly estimate NSF risks with gadodiamide. In one retrospective study of 370 patients with severe renal impairment who received gadodiamide, the estimated risk for development of NSF was 4%. The risk, if any for the

[1] A life-threatening event has been reported with this ADR.

development of NSF among patients with mild to moderate renal impairment or normal renal function is unknown, and the cautious utilization of the lowest possible dose of GBCA is preferable.

9 Drug Interactions

9.2 Drug Interactions Overview

No specific drug interaction studies have been done for AMBELVIST during the development of this product.

9.3 Drug-Behaviour Interactions

The interaction of AMBELVIST with individual behavioural risks (e.g. cigarette smoking, cannabis use, and/or alcohol consumption) has not been studied.

9.4 Drug-Drug Interactions

Non-clinical *in vivo* and *in vitro* studies showed no potential for drug-drug interactions.

No clinical interaction studies have been performed.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 Clinical Pharmacology

10.1 Mechanism of Action

Gadoquatrane is a paramagnetic tetramer molecule containing 4 macrocyclic non-ionic complexes of gadolinium, that develops a magnetic moment when placed in a magnetic field.

The magnetic moment alters the relaxation rates of water protons in its vicinity in the body, leading to an increase in signal intensity (brightness) of tissues.

10.2 Pharmacodynamics

In MRI, visualization of normal and pathological tissue depends in part on variations in the radiofrequency signal intensity that occur with:

- differences in proton density
- differences of the spin-lattice or longitudinal relaxation times (T1)
- differences in the spin-spin or transverse relaxation time (T2).

Gadoquatrane alters the T1 and T2 relaxation times in tissues in a magnetic field of an MRI scanner. The extent to which a contrast agent can affect the relaxation rate (1/T1 or 1/T2) of tissue water is termed relaxivity (r1 or r2). The relaxivities of gadoquatrane are presented in Table 5. Gadoquatrane exhibits high relaxivity due to its chemical structure. The linkage of 4 single gadolinium-chelates increases the molecular size leading to a slower rotational motion i.e. tumbling rate (τR).

Table 5: Relaxivities (L/mmol/sec) of gadoquatrane studied *in vitro* in human plasma at 37°C at 1.5 & 3T

Gadoquatrane		Relaxivity (r1)	Relaxivity (r2)
1.5 T	Per molecule	46.8	59.2
3.0 T	Per molecule	42.0	53.6

T = Tesla; Gadoquatrane contains 4 chelated gadolinium ions. The per gadolinium relaxivities (at 1.5T and 3.0T) r1 is 11.7/10.5 (L/mmol/sec) and r2 is 14.8/13.4 (L/mmol/sec), respectively.

Cardiac Electrophysiology

At 5 times the recommended dose of gadoquatrane, clinically significant QTc interval prolongation was not observed.

10.3 Pharmacokinetics

Gadoquatrane is administered as an intravenous injection. The peak plasma concentration (C_{max}) and area under the concentration time curve (AUC) of gadolinium (Gd) increased proportionally over a dose range from 0.0025 to 0.05 mmol/kg of gadoquatrane (0.25 to 5 times the recommended dose) (See Table 6).

Table 6: Pharmacokinetics parameters (median, (5^{th}, 95^{th} Percentile)) of gadoquatrane in adults.

Pharmacokinetic parameter	Median (5th, 95th percentile)
eGFR	105 (92, 126)
C_{max} (µmolGd/L)	397 (249, 628)
AUC (µmolGd*h/L)	421 (308, 651)
CL/BW (L/h/kg)	0.095 (0.062, 0.130)
V_{ss}/BW (L/kg)	0.205 (0.157, 0.249)
$t_{1/2,eff}$ (h)	1.47 (1.16, 2.24)
C_{10} (µmol Gd/L)	268 (209, 374)
C_{20} (µmol Gd/L)	216 (171, 295)
C_{30} (µmol Gd/L)	178 (142, 239)

C_{max} = Maximum concentration, AUC = area under the concentration versus time curve from zero to infinity; CL = clearance; BW=body weight; Vss/BW = volume of distribution at steady state normalized to body weight; $t_{1/2, eff}$ = effective half-life , C_{10} = Plasma concentration at 10 minutes post-dose; C_{20} = Plasma concentration at 20 minutes post-dose; Gd=gadolinium, C_{30} = Plasma concentration at 30 minutes post-dose.

Distribution

After intravenous administration, gadoquatrane is rapidly distributed from the vascular to the extracellular space. Plasma protein binding is negligible (<1%) in vitro.

For the clinical dose of 0.01 mmol/kg (0.04 mmol gadolinium/kg body weight) pharmacokinetics (PK) parameter estimates are summarized in Table 6.

Metabolism

Gadoquatrane is not metabolized.

Elimination

Gadoquatrane is eliminated rapidly from plasma via the kidneys in an unchanged form. Plasma clearance is similar to renal clearance and renal clearance of inulin, indicating elimination by glomerular filtration (See Table 6). On average, 90.7% (CV 12.7%) of the dose was excreted in the urine within 12

hours after intravenous administration, with only trace amounts thereafter (91.8% (CV 12.8%) after 72 h). Extrarenal elimination is negligible, less than 1 % was detectable in feces (See Table 6).

Special populations and conditions

Pediatrics (< 18 years of age)

No relevant impact of age on PK of gadoquatrane was observed. The PK profile of gadoquatrane in pediatric patients is similar to that observed in adults (See Table 7). No dose adjustment is required as early concentrations, relevant for imaging efficacy, are independent of age.

Table 7: PK parameters (median, (5^{th}, 95^{th} Percentile)) for gadoquatrane in pediatric and adult patients for a dose of 0.01 mmol/kg BW (corresponding to 0.04 mmol Gd/kg BW).

	0 to <2years	2-<12 years	12-<18 years	0 to <18 years	Adults (eGFR > 72)
eGFR (mL/min/1.73m²)	131 (74.7-179)	141 (101-192)	116 (85.6-155)	134 (85.1-186)	98.7 (76.6, 124)
AUC (µmol Gd*h/L)	287 (214-353)	250 (200-342)	347 (264-460)	284 (203-398)	462 (315, 766)
CL/BW (L/h/kg)	0.139 (0.113-0.190)	0.160 (0.116-0.202)	0.115 (0.0869-0.150)	0.142 (0.100-0.194)	0.0870 (0.0522, 0.127)
V_{ss}/BW (L/kg)	0.245 (0.226-0.259)	0.233 (0.199-0.244)	0.198 (0.171-0.230)	0.230 (0.175-0.251)	0.205 (0.157, 0.252)
$t_{1/2,eff}$ (h)	1.19 (0.928-1.52)	1.01 (0.829-1.28)	1.15 (1.04-1.34)	1.07 (0.844-1.40)	1.57 (1.18, 2.60)
C_{10} (µmol Gd/L)	184 (167, 199)	190 (175, 228)	236 (193, 268)	193 (168, 261)	269 (209, 375)
C_{20} (µmol Gd/L)	153 (135, 164)	156 (139, 193)	200 (161, 228)	160 (136, 220)	220 (172, 299)
C_{30} (µmol Gd/L)	127 (111, 140)	128 (109, 163)	169 (134, 195)	134 (110, 186)	181 (144, 246)

eGFR = estimated Glomerular Filtration Rate; AUC = area under the concentration versus time curve from zero to infinity; CL = clearance; BW=body weight; Vss/BW = volume of distribution at steady state normalized to body weight; $t_{1/2, eff}$ = effective half-life; C_{10} = Plasma concentration at 10 minutes post-dose; C_{20} = Plasma concentration at 20 minutes post-dose; Gd=gadolinium, , C_{30} = Plasma concentration at 30 minutes post-dose; Gd=gadolinium.

Geriatrics (≥ 65 years of age)

Due to age-related physiological changes in renal function, systemic exposure may be increased. No dose adjustment is required, as early concentrations, relevant for imaging efficacy, are independent of renal function.

Sex

No relevant impact of sex on the PK of gadoquatrane was observed.

Hepatic Insufficiency

Gadoquatrane is almost exclusively renally eliminated in an unchanged form. Therefore, hepatic impairment is unlikely to alter the PK of gadoquatrane.

Renal Insufficiency

Gadoquatrane is almost exclusively renally eliminated in an unchanged form.

A population pharmacokinetic (popPK) analysis in adult study populations (N=871), including 285 participants with mild and 58 participants with moderate renal impairment, was conducted. Gadolinium clearance decreased as the severity of renal impairment increased, leading to higher total drug exposure (AUC) and prolonged excretion time. Despite the effects on total exposure, early plasma concentrations were not affected by the subjects' level of renal function (See Table 8).

Table 8: PK parameters (Median, (5th, 95th Percentile)) of gadoquatrane with normal and impaired renal function in adults for a dose of 0.01 mmol/kg BW (corresponding to 0.04 mmol Gd/kg BW)

	Normal renal function (eGFR ≥90 [mL/min/1.73 m²])	**Mild renal impairment (eGFR ≥60-89 [mL/min/1.73 m²])**	**Moderate renal impairment (eGFR ≥30-59 [mL/min/1.73 m²])**	**Severe renal impairment (eGFR <30 [mL/min/1.73 m²])**
AUC (µmol Gd*h/L)	421 (308, 651)	576 (423, 908)	851 (579, 1315)	2016 (1252, 4283)[a]
V_{ss}/BW (L/kg)	0.205 (0.157, 0.249)	0.202 (0.158, 0.253)	0.193 (0.164, 0.226)	0.335 (0.246, 0.391)
CL/BW (L/h/kg)	0.095 (0.062, 0.130)	0.070 (0.044, 0.095)	0.047 (0.031, 0.069)	0.0198 (0.0093, 0.032)
$t_{1/2,eff}$ (h)	1.47 (1.16, 2.24)	1.97 (1.51, 3.25)	2.94 (1.84, 5.05)	11.3 (7.25, 24.0)
C_{10} (µmol Gd/L)	268 (209, 374)	279 (216, 382)	303 (242, 367)	304 (232, 427)[a]
C_{20} (µmol Gd/L)	216 (171, 295)	235 (186, 311)	266 (211, 314)	258 (204, 355)[a]
C_{30} (µmol Gd/L)	178 (142, 239)	199 (163, 262)	229 (185, 274)	228 (184, 312)

[a] Normalized to a dose level of 0.04 mmol Gd/kg; BW = body weight; AUC = Area Under the Curve; Vss = Volume of distribution at steady state; CL = Clearance; $t_{1/2, eff}$ = effective half-life; C_{10}: Plasma concentration at 10 minutes post-dose; C_{20}: Plasma concentration at 20 minutes post-dose; Gd=gadolinium; C_{30}: Plasma concentration at 30 minutes post-dose.

In patients with mild or moderate renal impairment, about 90% of the administered gadoquatrane was recovered in urine within 24 hours. In simulated patients with severely impaired renal function, recovery of a similar amount is anticipated in urine within 5-7 days. No clinical studies have been conducted in patients with severe renal impairment.

Gadoquatrane has been shown to be dialyzable in an in vitro hemodialysis study. After 1 hour of in vitro hemodialysis, approximately 97% of gadoquatrane was removed from the plasma.

11 Storage, Stability, and Disposal

AMBELVIST should be stored between 15°C and 30°C. Protect from freezing.

After the vial/bottle has been opened, chemical and physical in-use stability has been demonstrated for 24 hours at 20°C to 25°C. Any unused AMBELVIST or waste material should be disposed of in accordance with local requirements.

12 Special Handling Instructions

Use of vials: Draw AMBELVIST into the syringe immediately before use. The rubber stopper should never be pierced more than once.

Use of Pharmacy Bulk Packs: AMBELVIST pharmacy bulk packages are for intravenous use and not for direct infusion. The transfer of AMBELVIST from the pharmacy bulk package into syringes must be performed in an aseptic work area, using aseptic techniques. The contents of the pharmacy bulk package after initial puncture should be used within 24 hours.

For more information, See 4.1 Dosing Considerations and 4.4 Administration.

Part 2: Scientific Information

13 Pharmaceutical Information

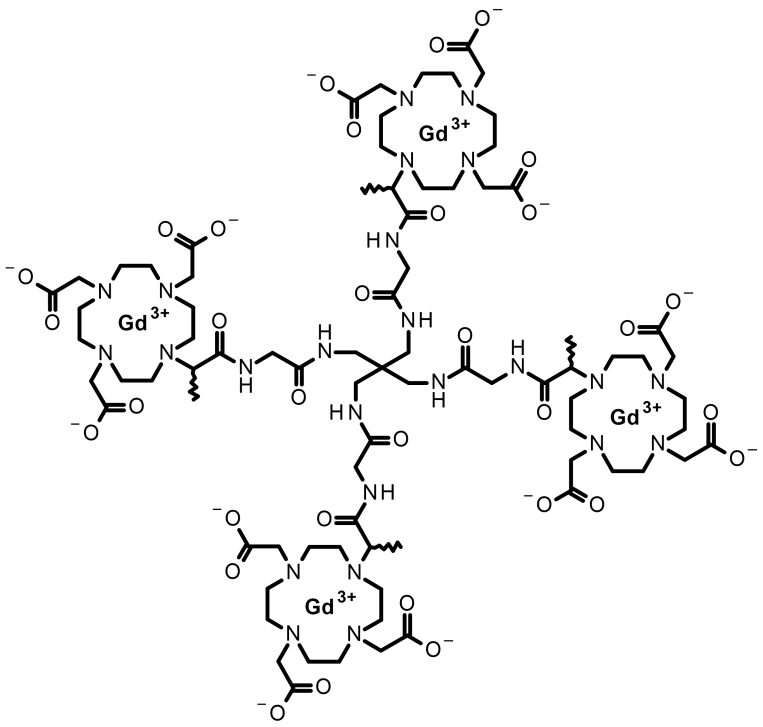
Drug Substance

Non-proprietary name of the drug substance(s): gadoquatrane

Chemical name: Tetragadolinium [4,10-bis(carboxylatomethyl)-7-{3,6,12,15-tetraoxo-16-[4,7,10-tris-(carboxylatomethyl)-1,4,7,10-tetraazacyclododecan-1- yl]-9,9-bis({[({2-[4,7,10-tris-(carboxylatomethyl)-1,4,7,10- tetraazacyclododecan-1-yl]propanoyl}amino)acetyl]-amino}methyl)- 4,7,11,14-tetraazaheptadecan-2-yl}-1,4,7,10-tetraazacyclododecan-1- yl]acetate

Molecular formula and molecular mass: $C_{81}H_{128}N_{24}O_{32}Gd_4$ and 257.9

Structure (for biologics)/Structural formula:



Chirality: mixture of three diastereomers. Gadoquatrane features four asymmetric carbons, resulting in three possible diastereomers. Diastereomer 1 (RSRS=SRSR, meso-compound), Diastereomer 2 (RRRS/SSSR, pair of enantiomers) and Diastereomer 3 (RRRR/SSSS, pair of enantiomers).

Physical form: a white or almost white, crystalline powder (hydrate).

Solubility: freely soluble in water, phosphate buffer (at pH 7 and 8), acetate buffer (at a pH 4.5) and hydrochloric acid. Very slightly soluble in ethanol, sparingly soluble in polyethylene glycol 400, soluble in dimethyl sulfoxide and practically insoluble in acetonitrile and acetone.

Density: 1.74 g/cm^3

14 Clinical Trials

14.1 Clinical Trials by Indication

Contrast enhanced magnetic resonance imaging of the Central Nervous System and Other Body Regions

Table 9: Summary of patient demographics for clinical trials in contrast enhanced magnetic resonance imaging (CE-MRI)

Study #	Study design	Dosage, route of administration and study duration	Study patients (n)*	Mean age (range)	Sex
QUANTI CNS (Study 21181)	Phase III, multicenter, double-blind randomized, active comparator, cross-over	AMBELVIST 0.04 mmol Gd/kg BW, IV or SoC‡0.1 mmol Gd/kg BW, IV. 6 days – 6 weeks.	AMBELVIST: n = 299 SoC‡: n =299	55.6 yrs (20-86 yrs)	Male: 42% Female: 58%
QUANTI OBR (Study 21197)	Phase III, multicenter, double-blind randomized, active comparator, cross-over	AMBELVIST 0.04 mmol Gd/kg BW, IV or SoC‡0.1 mmol Gd/kg BW, IV. 6 days – 6 weeks.	AMBELVIST: n = 398 SoC‡: n =400	56.2 yrs (18-89 yrs)	Male: 49% Female: 51%
QUANTI Pediatric (Study 21196)	Phase I/III, open-label, single-arm	AMBELVIST 0.04 mmol Gd/kg BW, IV. 7 (±1) days.	AMBELVIST: n = 93	7.13 yrs (28 days-17 yrs)	Male: 59% Female: 41%

Gd = gadolinium; BW = body weight; IV = intravenous; yrs = years

‡ Soc = Standard of Care (SoC) mGBCAs (gadobutrol, gadoterate meglumine/ gadoteric acid, gadoteridol)

* Includes all randomized participants who received at least one dose of the study intervention

The safety and efficacy of AMBELVIST were investigated in two pivotal Phase III studies, QUANTI CNS and QUANTI OBR and one Phase I/III study in pediatric patients QUANTI Pediatric. Both, QUANTI CNS and OBR were randomized, multi-center, double-blind, active comparator (standard of care), cross-over studies involving 715 adult patients (randomized 1:1, QUANTI CNS 305 and QUANTI OBR 410). The enrolled study population for the assessment of efficacy included patients who had a clinical indication to undergo CE-MRI for evaluation of a known or suspected clinical condition in any target organ (including blood vessels) of the CNS and the body. The QUANTI-CNS focused on CNS pathologies, while QUANTI-OBR addressed pathologies in any body region except the CNS. Participants were aged ≥18 years in QUANTI CNS and QUANTI OBR, while QUANTI Pediatric enrolled patients <18 years of age.

The main exclusion criteria for adult patients were those who were clinically unstable, had a concurrent/concomitant condition that may significantly alter image comparability, had severe renal insufficiency (<30 mL/min/1.73m^2) or acute kidney injury, bronchial asthma or a moderate to severe allergy-like reaction to any GBCA. For pediatric patients, exclusion criteria included a body weight <2500 g at screening/baseline, acute kidney injury, eGFR <80% of age adjusted normal renal function or a moderate to severe allergy-like reaction to any GBCA.

AMBELVIST was administered at a dose of 0.01 mmol/kg body weight (0.04 mmol gadolinium/kg body weight) compared to the standard of care macrocyclic GBCAs (mGBCAs) (gadobutrol, gadoterate meglumine/ gadoteric acid or gadoteridol) at standard dose of 0.1 mmol gadolinium/kg body weight in a random order, separated by 2 to 14 days (i.e., representing a reduction of 60% of Gd dose versus the study comparator dose of 0.1 mmol gadolinium/kg body weight).

Pre-contrast (unenhanced) and combined image sets (consisting of both pre-contrast and post-contrast for the same contrast agent) were independently evaluated by three independent central blinded readers. Each reader assessed up to five lesions per patient using the three visualization parameters as endpoints, scoring them for contrast enhancement, delineation and morphology using a 4-point or 3-point scale (PS) (for morphology): For the assessment of blood vessels, the heart and normal structures (in the absence of lesions) the nomenclature was adapted to: Vessel Lumen Enhancement (4-PS), Vessel Border Delineation (4-PS), Vascular Diameter/Dimensions (internal morphology) (3-PS); Lesion/pathology contrast enhancement, Lesion delineation, Lesion identification; Normal enhancing structures contrast enhancement, Normal enhancing structures border delineation, Normal enhancing structures internal morphology.

The following scores were used for each of the parameters: Contrast Enhancement (4-point scale), None, Moderate, Good, Excellent; Delineation (4-point scale) None, Moderate, Good, Excellent; Morphology (3-point scale) Poor, Moderate, Good.

The primary analysis is based on the Extended Full Analysis Set which included all randomized participants who have CE-MRI/MRA image sets that qualified for blinded reads and had both gadoquatrane and SoC comparator combined pre- and post- contrast image sets assessable.

The diagnostic performance of AMBELVIST and the standard of care MRI was evaluated based on the sensitivity of lesion detection and specificity for correct exclusion of lesions, compared to composite Standard of Truth (cSoT) derived from all available clinical information up to one month after the last study-related MRI.

QUANTI CNS

The primary objective in the QUANTI CNS study was to demonstrate non-inferiority of AMBELVIST to standard of care mGBCAs in CE-MRI. The primary endpoints were evaluated using individual reader

scale scores for the three visualization parameters: contrast enhancement, delineation, and morphology of combined pre- and post- AMBELVIST MRI and combined pre- and post-standard of care MRI. The key secondary objective was to demonstrate that non-inferior diagnostic performance of AMBELVIST to standard of care mGBCAs in CE-MRI. The key secondary endpoint assessed sensitivity for lesion detection and specificity for exclusion of lesions based on the evaluation of the combined pre- and post- AMBELVIST MRI and combined pre- and post- standard of care mGBCA MRI. All evaluations were conducted in a blinded independent central review (BICR) by three readers.

The secondary objective was to demonstrate superior efficacy of AMBELVIST compared to unenhanced MRI, based on the same endpoints as for the primary objective.

The study population was 64.7% White, 29.0% Asian, 2.3% Black or African American, 0.3% of multiple racial background, and for 3.6%, the racial background was not reported.

QUANTI CNS included 305 patients scheduled for MRI with known or suspected pathology of the CNS, such as benign or malignant tumors; inflammatory or infectious lesions; vasculature abnormalities; and malformation of the brain (89.4%), followed by spine (5.0%), and blood vessels (4.6%). Of these, 276 had assessable combined MR image sets for AMBELVIST and for standard of care mGBCAs. The majority of patients (44%) presented with brain tumors, of these meningioma with 25.6% was the most common, 6.6% with multiple sclerosis, 4.6% with headache or migraine and 44.8% presented with other pathologies as unspecified intracranial lesions, aneurysm, epilepsy and others. For patients who did not have a lesion, depending on image set and reader, normal structures were assessed in 16 to up to 71 participants.

Results

Non-inferiority was demonstrated for all three visualization parameters across all three readers in the population (N=276). The differences in mean scores (SoC mGBCAs minus AMBELVIST) were consistently small and close to zero, ranging from 0.09 to 0.13 for contrast enhancement, 0.01 to 0.07 for delineation, and 0.02 to 0.04 for morphology (See Table 10). For all parameters and readers, the upper limits of the 95% CI were well below the pre-specified non-inferiority margin of 0.35.

The key secondary objective to show non-inferior diagnostic performance of AMBELVIST versus SoC mGBCA CE-MRI based on sensitivity and specificity for the detection / exclusion of lesions were met, further supporting the primary objective. The non-inferiority assessment used a pre-specified margin of 10% for the upper bound of the 95% confidence interval of the difference between treatments. For sensitivity, non-inferiority was confirmed across all readers. For specificity, non-inferiority was shown for two of the three readers, fulfilling the pre-specified statistical criteria.
The results of multiple sensitivity analyses across all analysis populations were supportive of the main analyses results.

Superior diagnostic efficacy of combined AMBELVIST MRI compared to pre- contrast MRI was demonstrated across all three readers for lesion visualization parameters. Mean improvements ranged from 1.17 to 1.64 points for contrast enhancement, 0.22 to 1.14 points for border delineation, and 0.36 to 0.94 points for internal morphology (See Table 11).
All differences were statistically significant ($p<0.0001$) with lower limits of the 95% confidence intervals consistently above zero, confirming consistent enhancement effects across readers.

Table 10: QUANTI CNS: Non-inferiority analysis of visualization parameters for combined AMBELVIST MRI compared versus combined standard of care versus mGBCA MRI (N=276)

Reader	Treatment	Contrast Enhancement		Delineation		Morphology	
		Mean estimate (SE)	Non inferiority (95% CI) *	Mean estimate (SE)	Non inferiority (95% CI) *	Mean estimate (SE)	Non inferiority (95% CI) *
1	**AMBELVIST**	2.33 (0.066)		3.34 (0.037)		2.68 (0.028)	
	SoC‡	2.45 (0.066)		3.41 (0.037)		2.71 (0.028)	
	Difference **	0.12 (0.071)	**YES** (-0.015, 0.264)	0.07 (0.047)	**YES** (-0.021, 0.166)	0.03 (0.036)	**YES** (-0.038, 0.105)
2	**AMBELVIST**	2.59 (0.066)		3.63 (0.037)		2.87 (0.028)	
	SoC‡	2.72 (0.066)		3.68 (0.037)		2.91 (0.028)	
	Difference **	0.13 (0.071)	**YES** (-0.013, 0.265)	0.05 (0.047)	**YES** (-0.043, 0.144)	0.04 (0.036)	**YES** (-0.034, 0.109)
3	**AMBELVIST**	2.15 (0.066)		2.17 (0.037)		1.68 (0.028)	
	SoC‡	2.24 (0.066)		2.18 (0.037)		1.70 (0.028)	
	Difference **	0.09 (0.071)	**YES** (-0.049, 0.229)	0.01 (0.047)	**YES** (-0.086, 0.100)	0.02 (0.036)	**YES** (-0.054, 0.089)

SE = Standard Error; CNS = Central nervous system; mGBCA = macrocyclic GBCA

*Lower & upper Limit of 95% Confidence Interval Non inferiority is achieved when upper limit of the confidence interval for the difference is < 0.35 (non-inferiority margin); ‡ Soc = Standard of Care (SoC) mGBCAs (gadobutrol, gadoterate meglumine/ gadoteric acid, gadoteridol); ** Standard of care minus AMBELVIST.

Table 11: QUANTI CNS: Superiority analysis of visualization parameters for combined AMBELVIST MRI versus pre-contrast MRI on participant level (N=276)

Reader	Treatment	Contrast Enhancement		Delineation		Morphology	
		Mean estimate (SE)	Superiority * (p-value)	Mean estimate (SE)	Superiority* (p-value)	Mean estimate (SE)	Superiority* (p-value)
1	**AMBELVIST**	2.36 (0.047)		3.40 (0.034)		2.73 (0.031)	
	Pre-contrast	1.00 (0.047)		2.32 (0.034)		1.79 (0.031)	
	Difference**	**1.36** (0.061)	**YES** (<.0001)	**1.08** (0.045)	**YES** (<.0001)	**0.94** (0.042)	**YES** (<.0001)
2	**AMBELVIST**	2.64 (0.047)		3.69 (0.034)		2.91 (0.031)	
	Pre-contrast	1.00 (0.047)		2.56 (0.034)		2.20 (0.031)	
	Difference**	**1.64** (0.061)	**YES** (<.0001)	**1.14** (0.045)	**YES** (<.0001)	**0.72** (0.042)	**YES** (<.0001)
3	**AMBELVIST**	2.19 (0.047)		2.20 (0.034)		1.70 (0.031)	
	Pre-contrast	1.02 (0.047)		1.99 (0.034)		1.35 (0.031)	
	Difference**	**1.17** (0.061)	**YES** (<.0001)	**0.22** (0.045)	**YES** (<.0001)	**0.36** (0.042)	**YES** (<.0001)

SE = Standard Error; CNS = Central nervous system

*Superiority of AMBELVIST over pre- AMBELVIST is demonstrated if one sided p-value is less than 0.025;

** AMBELVIST minus Pre-contrast.

QUANTI OBR

The QUANTI OBR study had the same design as the QUANTI CNS study investigating the same objectives and endpoints.

The study population was 69.6% White, 26.7% Asian, 0.7% Black or African American and 2.2% the racial background was not reported.

QUANTI OBR included 410 patients with known or suspected pathology in other body regions, such as, head and neck, thorax, abdomen, pelvis and extremities. Of these, 379 had assessable MR combined image sets for AMBELVIST and for standard of care mGBCAs.

Patients presented with liver tumors (12.3%), prostate tumors (9.4%), breast tumors (8.9%), cardiac disorders (8.1% including cardiomyopathy with 3.2%), pancreatic pathologies (7.4%), uterine pathologies (5.7%), kidney tumors (4.9%), musculoskeletal diseases (4.7%), pathologies of the vascular system (4.2%) and others (34.4% representing a broad range of pathologies composed predominantly of isolated oncologic, gastrointestinal, head-and-neck, pulmonary, hematologic/systemic, and miscellaneous conditions, each generally reported in ≤1.2% of patients). For patients who did not have a lesion, depending on image set and reader, normal structures were assessed in 47 to up to 64 participants.

Results

In the phase III QUANTI OBR study, the primary objective, non-inferiority of AMBELVIST at 0.01 mmol/kg body weight compared to mGBCAs at 0.1 mmol/kg body weight (upper limit of 95% CI <0.35 for mean difference in treatment effects) was demonstrated; for all three visualization parameters and for all three reader groups, based on a linear mixed effects model for the overall population. The secondary objective, superiority of the combined pre-contrast and post-contrast MRI sets with AMBELVIST over pre-contrast MRI for the three lesion visualization parameters and all three reader groups (one-sided p-value <0.025) was demonstrated, based on a linear mixed effects model for the overall population.

Non-inferiority was demonstrated for all three visualization parameters across all three reader groups in the population (N=378). The differences in mean scores (SoC mGBCA minus AMBELVIST) were consistently small and close to 0, ranging from -0.06 to 0.03 for contrast enhancement, -0.06 to 0.02 for delineation, and -0.05 to -0.01 for Morphology (See Table 12). For all parameters and reader groups, the upper limits of the 95% CI were well below the pre-specified non-inferiority margin of 0.35.

The key secondary objective to show non-inferior diagnostic performance of AMBELVIST vs. SoC mGBCA MRI based on sensitivity and specificity for the detection / exclusion of lesions was met, further supporting the primary objective. The non-inferiority assessment used a pre-specified margin of 10% for the upper bound of the 95% confidence interval of the difference between treatments. For sensitivity, non-inferiority was confirmed across all reader groups. For specificity, non-inferiority was shown for two of the three reader groups, fulfilling the pre-specified statistical criteria.
The results of multiple sensitivity analyses across all analysis populations were supportive of the main analyses results.

Superior diagnostic efficacy of combined AMBELVIST MRI compared to pre- contrast MRI was demonstrated significant improvements in all visualization parameters compared to pre-contrast images. Mean improvements ranged from 2.12 to 2.70 points for contrast enhancement, 1.08 to 2.46 points for delineation, and 0.90 to 1.70 points for morphology (See Table 13). All differences were statistically significant (p<0.0001) with lower limits of 95% confidence intervals consistently above zero, confirming consistent enhancement effects across reader groups.

Table 12: QUANTI OBR: Non-inferiority analysis of visualization parameters combined AMBELVIST MRI versus combined standard of care mGBCAs MRI on participant level (N= 378)

Reader	Treatment	Contrast Enhancement		Delineation		Morphology	
		Mean estimate (SE)	Non inferiority (95% CI)*	Mean estimate (SE)	Non inferiority (95% CI) *	Mean estimate (SE)	Non inferiority (95% CI)*
1	**AMBELVIST**	3.63 (0.048)		3.68 (0.039)		2.85 (0.026)	
	SoC‡	3.57 (0.048)		3.62 (0.039)		2.80 (0.026)	
	Difference **	**-0.059** (0.062)	**YES** (-0.181, 0.062)	**-0.057** (0.050)	**YES** (-0.155, 0.042)	**-0.052** (0.035)	**YES** (-0.120, 0.017)
2	**AMBELVIST**	3.11 (0.048)		3.63 (0.039)		2.75 (0.026)	
	SoC‡	3.13 (0.048)		3.65 (0.039)		2.74 (0.026)	
	Difference **	**0.027** (0.062)	**YES** (-0.094, 0.149)	**0.023** (0.050)	**YES** (-0.075, 0.121)	**-0.012** (0.035)	**YES** (-0.080, 0.057)
3	**AMBELVIST**	3.26 (0.048)		3.38 (0.039)		2.74 (0.026)	
	SoC‡	3.23 (0.048)		3.35 (0.039)		2.73 (0.026)	
	Difference **	**-0.028** (0.062)	**YES** (-0.150, 0.094)	**-0.033** (0.050)	**YES** (-0.131, 0.065)	**-0.011** (0.035)	**YES** (-0.079, 0.058)

SE = Standard Error; OBR = other body regions; mGBCA = macrocyclic GBCA

*Lower & upper Limit of 95% Confidence Interval. Non inferiority is achieved when upper limit of the confidence interval for the difference is < 0.35 (non- inferiority margin); ‡Soc = Standard of Care (SoC) mGBCAs (gadobutrol, gadoterate meglumine/ gadoteric acid, gadoteridol); ** Standard of care minus AMBELVIST.

Table 13: QUANTI OBR: Superiority analysis of visualization parameters for combined AMBELVIST MRI versus pre-contrast MRI on participant level (N=378)

Reader	Treatment	Contrast Enhancement		Delineation		Morphology	
		Mean estimate (SE)	Superiority* (p-value)	Mean estimate (SE)	Superiority* (p-value)	Mean estimate (SE)	Superiority* (p-value)
1	**AMBELVIST**	3.80 (0.035)		3.85 (0.034)		2.96 (0.024)	
	Pre-contrast	1.10 (0.035)		1.39 (0.034)		1.27 (0.024)	
	Difference**	**2.70** (0.047)	**YES** (<.0001)	**2.46** (0.047)	**YES** (<.0001)	**1.70** (0.033)	**YES** (<.0001)
2	**AMBELVIST**	3.23 (0.035)		3.83 (0.034)		2.89 (0.024)	
	Pre-contrast	1.11 (0.035)		2.75 (0.034)		1.98 (0.024)	
	Difference**	**2.12** (0.047)	**YES** (<.0001)	**1.08** (0.047)	**YES** (<.0001)	**0.90** (0.033)	**YES** (<.0001)
3	**AMBELVIST**	3.39 (0.035)		3.51 (0.034)		2.84 (0.024)	
	Pre-contrast	1.05 (0.035)		1.64 (0.034)		1.17 (0.024)	
	Difference**	**2.35** (0.047)	**YES** (<.0001)	**1.86** (0.047)	**YES** (<.0001)	**1.67** (0.033)	**YES** (<.0001)

SE = Standard Error; OBR = other body regions

*Superiority of AMBELVIST over pre-AMBELVIST is demonstrated if one sided p-value is less than 0.025;

**AMBELVIST minus Pre-Contrast

QUANTI Pediatric

The primary objective in the Pediatric study was to evaluate the pharmacokinetic (PK) and safety of AMBELVIST in a multicenter, prospective, open-label Phase I/III study (QUANTI-Pediatric). The study included 93 pediatric patients from birth to <18 years who had a clinical indication to undergo a CE-MRI in any body region. The body regions for MRI examination were the brain (62.4%), abdominal cavity (10.8%), spine (8.6%), extremities (7.5%), head and neck (3.2%), pelvis (3.2%) and thorax (2.2%). The study population was 57% White, 37.6% Asian, 1.1% Black or African American and for 4.3% no racial background was reported.

Patients presented with current or historical tumor-related and non-tumor-related conditions, including brain tumors (31.2%), abdominal cavity tumors/metastasis (9.7%), other tumors (7.5%), epilepsy/seizures (7.5%), spine tumors (6.5%), extremity tumors (5.4%), multiple sclerosis/demyelinating disease (4.3%), neurofibromatosis type 1 (3.2%) and other (24.7% heterogeneous single cases which comprised vascular conditions such as sinus vein thrombosis, vein of Galen malformation, and vascular malformation of the neck; inflammatory/infectious or demyelinating conditions such as tuberculous meningitis and demyelinating disease; congenital or structural abnormalities such as Apert syndrome, diaphragmatic hernia, and sacrococcygeal cyst; and clinical/symptom-based indications including headache, vision abnormalities, psychobehavioural abnormality, circulatory collapse, growth retardation, GRIN2B mutation, and thigh hypertrophy. Additional hematologic or histiocytic diagnoses such as acute lymphocytic leukemia and Langerhans

cell histiocytosis were also listed). Overall, pathologies were visible in 62/93 participants (65.6%), no pathology was identified in 31/93 participants (34.4%).

The patients received AMBELVIST at a dose of 0.01 mmol/kg body weight (0.04 mmol gadolinium/kg body weight) and were assigned to three age groups: birth to <2 years, 2 to <12 years, and 12 to <18 years.

The PK and safety profiles in pediatric patients were similar in all age groups and to those observed in adult patients (See 10.3 Special populations and conditions – Pediatrics).

MR images were assessed using qualitative parameters in explorative manner. For all parameters (e.g. diagnostic confidence, visualization parameters and others) there was an improvement with the post AMBELVIST MRI versus the pre-contrast MRI. There were no relevant differences among the pediatric age groups.

15. Microbiology

No microbiological information is required for this drug product.

16 Non-Clinical Toxicology

General toxicology

Experimental systemic toxicity studies in rats and monkeys following single (up to 6 mmol gadolinium/kg in rats and 3 mmol gadolinium/kg in monkeys) and repeated (4 weeks: 1.55 mmol gadolinium/kg/day) daily intravenous administration produced no treatment-related adverse findings. The rat single-dose and repeat-dose no observed adverse effect level (NOAEL) was 6.0 mmol Gd/kg (16 times the Recommended Human Dose based on AUC (RHD)) and 1.55 mmol Gd/kg (4 times the RHD), respectively. The monkey single-dose and repeat-dose NOAEL was 3.0 mmol Gd/kg (49 times the RHD) and 1.55 mmol Gd/kg (16x the RHD), respectively.

Safety Pharmacology

Single intravenous bolus injection of gadoquatrane (at dose levels up to 1.6 mmol gadolinium/kg in rats and 1.2 mmol gadolinium/kg in monkeys) had no physiologically relevant effect on parameters of vital and supplemental organ function of rats and monkeys. The corresponding plasma exposure in terms of C_{max} was approximately 10 (rat) to 24 times (monkey) higher than the C_{max} at the recommended single human diagnostic dose.

Genotoxicity

Studies of genotoxic effects (gene-, chromosomal- and genome mutation tests) of gadoquatrane *in vivo* and *in vitro* gave no indication of a mutagenic potential.

Carcinogenicity

No studies on the carcinogenic potential of AMBELVIST were performed.

Reproductive and developmental toxicology

In the fertility and early embryonic development toxicity study in rats, gadoquatrane was administered at dose levels up to 1.55 mmol gadolinium/kg/day to male and female rats. The NOAEL for male and female fertility was 1.55 mmol gadolinium/kg/day (12 to 20 time the RHD). Gadoquatrane showed a potential female-mediated, borderline effect on embryonic survival, evidenced as a minimal increase in the mean number of dead embryos and percent post implantation loss at 1.55 mmol gadolinium/kg/d (12 times the RHD). The rat early-embryonic NOAEL was 0.56 mmol Gd/kg (4 times the RHD).

Gadoquatrane did not cause embryofetal toxicity or teratogenicity when given repeatedly during organogenesis at doses up to 1.55 mmol gadolinium/kg/day to rats and rabbits. The exposure at the high dose (NOAEL) was 18 to 23 times the RHD. Placental transfer was demonstrated in the rat and rabbit embryo-fetal development studies as gadolinium was detected in the pup plasma.

When rats were treated through pregnancy and lactation at doses up to 1.55 mmol gadolinium/kg/day, there were no adverse effects on survival, growth, sexual maturation, neurobehavioral and reproductive function in the offspring. The exposure at the high dose corresponded to 12 to 38 times the RHD. Small amounts of gadoquatrane were excreted with the milk. (See 7.1.1 Pregnancy and 7.1.2 Breastfeeding).

Juvenile toxicity

Single and repeat-dose toxicity studies in juvenile rats at doses of up to 1.8 mmol gadolinium/kg/day did not reveal any adverse findings. The exposure reached in these studies represent 23 to 27 times the RHD.

Special toxicology

Gadoquatrane was tolerated following repeated intravenous administration and single intravenous and perivascular administration without adverse local effects.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

AMBELVIST®

gadoquatrane injection

This Patient Medication Information is written for the person who will be given **AMBELVIST**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **AMBELVIST**, talk to a healthcare professional.

Serious warnings and precautions box

Gadolinium-based contrast agents (such as AMBELVIST) increase the risk of getting a rare and severe disease called **Nephrogenic Systemic Fibrosis (NSF)** in patients with:

- Chronic, severe kidney disease, or
- Acute kidney injury.

In NSF, the skin becomes thickened, coarse and hard, which makes bending of the joints difficult. NSF may spread to other parts of the body such as your muscles and organs and even cause death. Your healthcare professional will screen you for kidney problems before you are given AMBELVIST. They will avoid giving AMBELVIST to you if you have certain kidney problems unless it is absolutely necessary. They will make sure to give you the right dose and will wait longer before giving you AMBELVIST again. See also "**Other warnings you should know about**", further below, for more information.

Not for Intrathecal Use

If injected into the spinal canal (by intrathecal injection), gadolinium-based contrast agents such as AMBELVIST can cause serious life-threatening side effects such as:

- Coma (prolonged loss of consciousness)
- Encephalopathy (changes in how your brain works)
- Seizures (temporary loss of consciousness and muscle control)
- Death

AMBELVIST is for intravenous (IV) use only.

What AMBELVIST is used for:

AMBELVIST is a contrast agent for magnetic resonance imaging (MRI) of the body including the brain and spine. It is used in adults and in children of all ages.

How AMBELVIST works:

MRI is a form of medical diagnostic imaging that creates detailed images of the organs and tissues inside your body. AMBELVIST makes certain areas appear brighter in your MRI. This helps your healthcare professional see any issues.

The ingredients in AMBELVIST are:

Medicinal ingredient: gadoquatrane

Non-medicinal ingredients: calcobutrol, hydrochloric acid, sodium chloride, trometamol and water for injection.

AMBELVIST comes in the following dosage forms:

Solution; 257.9 mg / mL (0.1 mmol / mL) gadoquatrane.

Do not use AMBELVIST if:

- You are allergic to gadoquatrane or to any of the other ingredients in AMBELVIST.
- You are allergic to any part of the AMBELVIST container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you receive AMBELVIST. Talk about any health conditions or problems you may have, including if you:

- Have had an allergic reaction to contrast agent in the past.
- Have or have had an allergy such as hay fever in the past.
- Have or have had asthma in the past.
- Have or have had a brain condition with seizures in the past.
- Have kidney problems. Your healthcare professional may take blood tests to decide if you should be given AMBELVIST.
- Have had a liver transplant in the last few months, or soon will have one.

Other warnings you should know about:

Accumulation of Gadolinium in the Brain

Gadolinium which is in AMBELVIST may accumulate (build-up) in the brain after multiple administrations. It is not known how this may affect the brain. Your healthcare professional will carefully consider whether to use repeat doses of AMBELVIST and will use the lowest dose necessary.

Nephrogenic Systemic Fibrosis

Receiving AMBELVIST may cause Nephrogenic Systemic Fibrosis (NSF). This is a rare condition which has only been observed so far in patients with kidney problems. NSF causes the skin to become thickened, coarse and hard, which sometimes makes bending of the joints difficult. NSF may spread to other organs and even cause death.

Your healthcare professional will screen you for kidney problems before you are given AMBELVIST. Tell your healthcare professional before you receive AMBELVIST if you know you have any kidney problems. You must get immediate medical help if you get any symptom of NSF after you receive AMBELVIST. These include: skin changes including hardening, thickening, burning, itching, scaling, darkening and tightening of the skin, red or dark patches on the skin, stiffness in the joints with trouble moving, pain in the hip bones or ribs, severe pain, muscle weakness. Also tell your healthcare professional if you have ever had symptoms of NSF after receiving MRI in the past.

Your healthcare professional will monitor your health after administering AMBELVIST.

Your healthcare professional will make sure that AMBELVIST has been removed from your body before you receive a second injection of AMBELVIST.

AMBELVIST can be removed from the body by dialysis. If you are currently on dialysis, your healthcare professional will decide when you should receive your next dialysis.

Serious Allergic Reaction

AMBELVIST can cause a serious allergic reaction. Patients who have had an allergic reaction to a contrast media agent in the past are at a greater risk. Most reactions occur within 30 minutes after receiving AMBELVIST. However, they can also happen within hours or days after receiving AMBELVIST. Your healthcare professional will monitor you for a period of time after you have received AMBELVIST. See also **Serious side effects and what to do about them**, further below, for symptoms and what to do if you experience them.

Pregnancy

Tell your healthcare professional before you receive AMBELVIST if you are pregnant, think you are pregnant or are planning to have a baby. It is not known if AMBELVIST may harm your unborn baby. Your healthcare professional will decide with you whether you should receive AMBELVIST.

Breastfeeding

Before you receive AMBELVIST tell your healthcare professional if you are breastfeeding or plan to breastfeed. It is not known if AMBELVIST passes into breast milk.

Your healthcare professional will decide if you should stop breastfeeding for 24 hours after you receive AMBELVIST and will discuss this with you.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take AMBELVIST:

- AMBELVIST will be given to you by a healthcare professional.
- It will be infused directly into your vein.
- It will be given to you before your MRI procedure.
- Follow all instructions given to you by your healthcare professional.

Usual dose:

Your healthcare professional will decide how much AMBELVIST you will receive. The dose you receive will be based on your weight. The usual dose of AMBELVIST is 0.1 mL per 1 kg body weight.

Overdose:

If you think you, or a person you are caring for, have been given too much AMBELVIST, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Possible side effects from using AMBELVIST:

These are not all the possible side effects you may have when taking AMBELVIST. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Pain, redness, bruising, coldness or swelling where AMBELVIST was injected into your body
- Headache
- Dizziness, tingling or numbness

- Fever, feeling hot, cold or very warm
- Redness of the skin, itching
- Feeling sick to your stomach, throwing up, stomach discomfort or stomach pain
- Joint pain, pain or discomfort in an arm or leg, nose pain

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Uncommon			
Serious allergic reaction: swelling of the face, lips, tongue, eyes or throat, difficulty breathing, blueness in the lips, coughing, sneezing, runny nose, feeling lightheaded, chest pain, rash or hives, and redness or paleness in the skin. This can sometimes be fatal.		✓	
Unknown			
Nephrogenic Systemic Fibrosis (NSF) (a severe disease where skin becomes thickened, coarse and hard): skin changes including hardening, thickening, burning, itching, scaling, darkening, hardening and tightening of the skin, red or dark patches on the skin, stiffness in the joints with trouble moving, pain in the hip bones or ribs, severe pain, muscle weakness, effects on the normal working of internal organs which may potentially be life threatening.		✓	
Acute kidney injury (sudden and severe kidney problems): urinating less often than usual, fatigue, nausea or vomiting, itchiness or rashes, swelling in legs or feet, puffiness in the face or hands, weight gain, confusion.		✓	
Seizure (sudden change in brain activity): shaking or jerking uncontrollably, loss of awareness or consciousness, confusion, collapse.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

AMBELVIST should be stored at temperatures between 15°C to 30°C. Do not freeze.

After the vial or bottle has been opened, AMBELVIST is stable for 24 hours at 20°C to 25°C and must then be discarded.

Keep out of reach and sight of children.

If you want more information about AMBELVIST:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drugproducts/drug-product-database.html); the manufacturer's website (http://www.bayer.ca) or by calling Bayer Medical Information at 1-800-265-7382 or emailing canada.medinfo@bayer.com.

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