NEW DRUG APPROVAL

Brand Name	Bludigo™
Generic Name	indigotindisulfonate sodium
Drug Manufacturer	Provepharm Inc.

New Drug Approval

FDA approval date: July 8, 2022

Review designation: Standard

Type of review: Type 7 – Drug Already Marketed without Approved NDA; New Drug Approval (NDA): 216264

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Various forms of contrast media have been used to improve medical imaging. Their value has long been recognized, as attested to by their common daily use in imaging departments worldwide. Like all other pharmaceuticals, however, these agents are not completely devoid of risk. The major purpose of this manual is to assist radiologists in recognizing and managing the small but real risks inherent in the use of contrast media.

Adverse side effects from the administration of contrast media vary from minor physiological disturbances to rare severe life-threatening situations. Preparation for prompt treatment of contrast media reactions must include preparation for the entire spectrum of potential adverse events and include prearranged response planning with availability of appropriately trained personnel, equipment, and medications. Therefore, such preparation is best accomplished prior to approving and performing these examinations. Additionally, an ongoing quality assurance and quality improvement program for all radiologists and technologists and the requisite equipment are recommended. Thorough familiarity with the presentation and emergency treatment of contrast media reactions must be part of the environment in which all intravascular contrast media are administered.

Millions of radiological examinations assisted by intravascular contrast media are conducted each year in North America. Although adverse side effects are infrequent, a detailed knowledge of the variety of side effects, their likelihood in relationship to pre-existing conditions, and their treatment is required to insure optimal patient care.

As would be appropriate with any diagnostic procedure, preliminary considerations for the referring physician and the radiologist include:

1. Assessment of patient risk versus potential benefit of the contrast-assisted examination.
2. Imaging alternatives that would provide the same or better diagnostic information.
3. Assurance of a valid clinical indication for each contrast medium administration.

Because of the documented low incidence of adverse events, intravenous injection of contrast media may be exempted from the need for informed consent, but this decision should be based on state law, institutional policy, and departmental policy.

Efficacy

The safety and efficacy of Bludigo™ were evaluated in a randomized intra-patient controlled, blind to dose of Bludigo™, multi-center study (NCT04228445) in 118 adult patients undergoing endoscopic urological or gynecological surgical procedures including cystoscopic (58%), robotic (28%), and transvaginal (14%) approaches.

The majority of patients were white (89%), female (74%), and younger than 65 years of age (70%). Mean age was 51 years, and age ranged from 20 to 88 years.

Patients were randomized in a 1:1 ratio to receive 2.5 mL or 5 mL of Bludigo™ intravenously prior to the end of the surgical procedure. Each patient underwent cystoscopy and received 5 mL of sodium chloride injection 0.9% followed by the randomized Bludigo™ dose for visualization of urinary flow from the ureteral orifices. The 2.5 mL dose is not approved.

The ureteral orifices and urine flow were observed and video recorded from 0 to 10 minutes post injection, with separate recordings made following sodium chloride injection and Bludigo™. The conspicuity of the urine flow from the ureteral orifices was assessed in a randomized, blinded fashion by two independent central reviewers using a 5-point scale (1 = no urine flow observed; 2 = weak urine flow, little color contrast; 3 = Color contrast or significant urine flow; 4 = strong urine flow with good color contrast; and 5 = strong urine flow with striking contrast in color) once after sodium chloride injection and twice after Bludigo™ resulting in paired data. The surgeons also reviewed and scored conspicuity of the urine flow from the ureteral orifices.

The responder for a ureter is defined as the difference in conspicuity score between Bludigo™ and sodium chloride injection being at least one point difference and the conspicuity score following Bludigo™ alone being greater than or equal to three. The reviewer agreement with the responder endpoint is acceptable. The proportion of responders along with its 95% confidence interval by ureter and reviewer or surgeon is summarized in Table 1.

Table 1. Summary of Proportion of Responders by Ureter and Reviewer or Surgeon in Patients Receiving Bludigo™ 5 mL

	Bludigo™ 5 mL	
	Left Ureter (n=49)	Right Ureter (n=49)
Reviewer 1 % Responder* 95% CL**	63% (48%, 77%)	76% (61%, 87%)
Reviewer 2 % Responder 95% CL	78% (63%, 88%)	82% (68%, 91%)
Surgeon % Responder 95% CL	71% (57%, 83%)	82% (68%, 91%)

* responder: IC conspicuity score ≥ 3 and difference (IC – Saline) in conspicuity score ≥1, missing data is imputed as nonresponder

** two-sided 95% confidence limits for the proportion of responder, calculated using the Clopper-Pearson (Exact) method

Safety

ADVERSE EVENTS

Clinical Trials Adverse Reactions Reported

The safety of Bludigo™ was evaluated in a randomized, intra-patient controlled, blind to dose of Bludigo™, clinical trial. A total of 118 adult patients undergoing endoscopic urological or gynecological procedures were treated intravenously; 58 (49%) of these patients received one dose of Bludigo™ 2.5 mL and 60 (51%) of patients received one dose of Bludigo™ 5 mL. The 2.5 mL dose is not approved. The mean age of patients was 51 years, and 35 (30%) patients were 65 years of age or older. The majority of patients were White 105 (89%) and female 87 (74%).

The adverse reactions (≥1%) reported in the clinical trial are provided in Table 2.

Table 2. Adverse Reactions Reported at ≥ 1% of Patients Receiving Bludigo™ 5 mL Intravenously	
Constipation	3 (5.0)
Nausea	2 (3.3)
Vomiting	2 (3.3)
Abdominal Pain	2 (3.3)
Pyrexia	2 (3.3)
ALT increase	2 (3.3)
Dysuria	1 (1.7)

Additional Postmarketing Adverse Reactions Reported
Cardiovascular disorders: cardiac arrest, arrhythmia, asystole, atrioventricular block second degree, hypotension, elevation in blood pressure, bradycardia, tachycardia
General disorders and administration site conditions: injection site discoloration
Immune system disorders: anaphylactic reactions with hypotension, dyspnea, bronchospasm, urticaria, erythema

WARNINGS & PRECAUTIONS

Cardiovascular Reactions
Severe or life-threatening cardiovascular reactions including cardiac arrest, arrhythmia, asystole, second degree atrioventricular block, hypotension, elevation in blood pressure, bradycardia, and tachycardia have been reported generally within 60 minutes following administration of indigotindisulfonate sodium injection products and required urgent intervention.
Indigotindisulfonate may cause vasoconstriction by interference with vasodilation mediated by nitric oxide dependent mechanisms and by direct vasoconstriction. Indigotindisulfonate may also cause hypotension. Patients with hypertension, heart rate and conduction disorders, or medications causing bradycardia may be at increased risk for elevated blood pressure, hypotension, and bradycardia.

Closely monitor blood pressure and cardiac rhythm during and following the injection of Bludigo™. Interrupt administration if reactions are observed.

Hypersensitivity Reactions
Serious anaphylactic reactions with hypotension, dyspnea, bronchospasm, urticaria, or erythema have been reported with the use of indigotindisulfonate sodium injection products. Bludigo™ is contraindicated in patients with known hypersensitivity to indigotindisulfonate. Monitor patients for anaphylactic reactions and have emergency equipment and trained personnel readily available.

Interference with Oximetry Measurements
Indigotindisulfonate has been reported to interfere with light absorption and transiently interfere with pulse oximetric methods. Anesthesiologists should be aware of the potential for artifactual reduction in SpO2 when anesthetized patients are administered Bludigo™.

CONTRAINDICATIONS

Bludigo™ is contraindicated in patients with known hypersensitivity to indigotindisulfonate or any of its components.

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Clinical Pharmacology

MECHANISMS OF ACTION

Indigotindisulfonate is a dye excreted by the kidney through tubular secretion and enhances visualization of the ureteral orifices by its deep blue color.

Dose & Administration

ADULTS

The recommended dose of Bludigo™ is 5 mL given as an intravenous injection over 1 minute.

PEDIATRICS

The safety and effectiveness of Bludigo™ have not been established in pediatric patients.

GERIATRICS

Refer to adult dosing

RENAL IMPAIRMENT

Severe renal impairment (eGFR < 30 mL/min): Use of Bludigo™ is not recommended.

HEPATIC IMPAIRMENT

N/A

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection: 40 mg/5 mL (8 mg/mL) in a single-dose glass ampule.