Product Name	OPDIVO
Active substance	Nivolumab
Indication and conditions of use	The aim of this Medical Need Program is to make nivolumab available to adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin. Eligible patients, in the opinion and the clinical judgment of the treating physician, would benefit from a treatment with the product which does not have a marketing authorization yet in this indication. Dosage and route of administration: The patient will receive nivolumab 3 mg/kg administered intravenously over 60 minutes every 2 weeks. Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability. Guidelines for permanent discontinuation or withholding of doses are described in the protocol.

Conditions, delays and further rules for participation of patients	**1.1. <u>Mandatory Inclusion Criteria</u>:**
	- The patient is not eligible for a clinical trial running with nivolumab and/or a clinical trial running in the envisaged indication of this program.
	- The patient cannot be satisfactorily treated with the approved and commercially available alternative treatments, in accordance with clinical guidelines, because of efficacy and/or safety issues.
	- Before any program procedures are performed, the details of the program will be described to the patient, and the patient will be given a written informed consent document to read. If the patient agrees to participate in the program, consent will be indicated by signing and dating of the informed consent document in the presence of program personnel. This must be obtained before any program-related procedures that are not part of normal patient care can be completed.
	- ECOG Performance Status of ≤ 2.
	- Patients with histologically confirmed classical Hodgkin lymphoma who fulfill the following criteria are eligible:
	  ○ Patients who failed ASCT AND brentuximab vedotin
	  OR
	  ○ Patients who are unsuitable for ASCT and have failed at least 2 prior treatments.
	- Patients with prior allogeneic transplant who fulfill the above criteria and all of the following criteria are eligible:
	  ○ 6 or more months have lapsed since allogeneic stem cell transplant
	  ○ No history of acute GVHD
	  ○ No history of extensive or Grade 4 chronic GVHD
	  ○ Without immunosuppressive therapy for a minimum of 4 weeks and no clinically apparent GVHD
	  ○ There is no local study of nivolumab post-allogeneic SCT for enrollment for which this patient qualifies
	- Screening laboratory values must meet the following criteria (using CTCAE v4):
	  ○ WBC $\geq 2000/\mu L$
	  ○ Neutrophils $\geq 1500/\mu L$
	  ○ Platelets $\geq 100 \times 10^3/\mu L$

- Hemoglobin ≥ 9.0 g/dL
- Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance ≥ 50 mL/min (using the Cockcroft Gault formula)

  Female CrCl = $\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$

  Male CrCl = $\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$
- AST/ALT ≤ 3.0 x ULN
- Total bilirubin ≤ 1.5 x ULN except patients with Gilbert Syndrome who must have a total bilirubin level < 3.0 mg/dL).

- Males and females ≥ 18 years of age
- Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of investigational product
- Women must not be breastfeeding
- Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab plus 5 half-lives of nivolumab program drug (5 times the half-life = 125 days) plus 30 days (duration of ovulatory cycle) for a total of 155 days or 24 weeks post-treatment completion.
- Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab plus 5 half-lives of the program drug (125 days) plus 90 days (duration of sperm turnover) for a total of 31 weeks post-treatment completion. In addition, male patients must be willing to refrain from sperm donation during this time.
- Azoospermic males are exempt from contraceptive requirements. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements and must still undergo pregnancy testing.

  Physicians shall counsel WOCBP patients and male patients who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. At a minimum, contraceptive counseling should be provided at the time of assent or consent. Physicians shall advise on the use of highly effective methods of contraception, which have a failure rate of < 1% when used consistently and correctly.

  At a minimum, patients must agree to the use of 1 highly effective method of contraception as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. WOCBP and female partners of male patients who are WOCBP are expected to use 1 of the highly effective methods of contraception listed below. Male patients must inform their female partners who are WOCBP of the contraceptive requirements of this Guidance Document and are expected to adhere to using contraception with their partner. Contraception methods are as follows:

1. Progestogen only hormonal contraception associated with inhibition of ovulation.
2. Hormonal methods of contraception including oral contraceptive pills containing combined estrogen + progesterone, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena®
3. Nonhormonal IUDs, such as ParaGard®
4. Bilateral tubal occlusion
5. Vasectomised partner with documented azoospermia 90 days after procedure

- Vasectomised partner is a highly effective birth control method provided that the partner is the sole sexual partner of the WOCBP patient and that the vasectomised partner has received medical assessment of the surgical success.

6. Intrauterine hormone-releasing system (IUS).
7. Complete abstinence

- Complete abstinence is defined as the complete avoidance of heterosexual intercourse.
- Complete abstinence is an acceptable form of contraception for all program drugs and must be used throughout the duration of program (plus 5 half-lives of the investigational product plus 30 days).
- It is not necessary to use any other method of contraception when complete abstinence is elected.
- Patients who choose complete abstinence must continue to have pregnancy tests.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the patient chooses to forego complete abstinence.
- The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

UNACCEPTABLE METHODS OF CONTRACEPTION.

1) Periodic abstinence (calendar, symptothermal, post-ovulation methods)
2) Withdrawal (coitus interruptus)
3) Spermicide only
4) Lactation amenorrhea method (LAM) are not acceptable methods of contraception.

1.2.<u>Mandatory Exclusion Criteria:</u>

- Patients with untreated CNS metastases are excluded.
  Patients are eligible if CNS metastases are adequately treated and patients are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to first dose of program medication. In addition, patients must be either off corticosteroids, or on a stable or decreasing dose of $\leq$ 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to first dose of program medication.
- Patients must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before first dose of program medication.
- Patients with previous malignancies (except non-melanoma skin cancers, and in situ cancers such as the following: bladder, gastric, colon, cervical/dysplasia, melanoma, or breast) are excluded unless a complete remission was achieved at least 2 years prior to first program dose and no additional therapy is required or anticipated to be required during the program period.
- Other active malignancy requiring concurrent intervention.
- Patients with an active, known or suspected autoimmune disease. Patients with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
- Patients who have not been previously treated with an allogeneic STC and have a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of first program dose. Inhaled or topical steroids, and adrenal replacement steroid > 10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease.

	- Patients with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity. - Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). - Known medical condition that, in the physician's opinion, would increase the risk associated with program participation or program drug administration or interfere with the interpretation of safety results. - Prior experience in a BMS-sponsored, anti-PD-1, Phase 3 study - Presence of toxicities attributed to prior anti-cancer therapy other than alopecia, fatigue, or peripheral neuropathy that have not resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of program drug. - Chest radiation within 24 weeks - Previous carmustine 600 mg/m^2 as part of pre-transplant conditioning - History of severe hypersensitivity reactions to any monoclonal antibodies - History of allergy or intolerance (unacceptable adverse events) to program drug components or Polysorbate-80-containing infusions - Patients who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness Eligibility criteria for this program have been carefully considered to ensure the safety of the program patients. It is imperative that patients fully meet all eligibility criteria. **Process to include patients:** 1- Physician declaration and eligibility form : - Written request of the treating physician 2- Completed and signed ICF 3-Positive advice by the responsible physician 4-Confirmation of enrolment by the responsible physician Bristol-Myers Squibb will evaluate the eligibility of the patient and inform the requestor. Rejection or approval will be sent to the requesting physician within the 10 working days. If the request has been approved, the physician will receive this Medical Need Program protocol and all the procedural documents.

Duration of the program	The inclusion of patients does not depend on a cohort decision, patients will be accepted as soon as the program is authorized. Nivolumab will be provided free of charge by Bristol-Myers Squibb on an individual patient basis following the criteria stated in this program until reimbursement of the product is available in Belgium in the envisaged indication or until, in the clinical judgment of the treating physician, the patient is no longer benefiting from continuation of the treatment, until disease progression or unacceptable toxicity, whichever is sooner. Treatment duration must be in line with the supporting clinical trials. In case of reimbursement, no new patients will be allowed to enter the program, AND patients that are receiving treatment as part of the program will be switched to receive commercial supply. In case of non-reimbursement after one year following the sought approval of the classical Hodgkin Lymphoma indication in the nivolumab Marketing Authorisation by the European Commission, no new patients will be allowed to enter the program. However, patients that are receiving treatment as part of the program will continue to receive the treatment until the criteria for this discontinuation have been met (progression of disease or unacceptable toxicity) or reimbursement will be obtained. BMS reserves the right to terminate the MNP to the drug if any of the following occur: (1) The marketing application is rejected by the responsible health authority; (2) the product application is withdrawn due to safety concerns. BMS can decide at any moment to terminate the enrolment of new patients to the Medical Need Program.
Conditions of distribution	If the patient is eligible and the inclusion approved by the responsible physician, then the patient can receive nivolumab from the treating physician.
Responsible of the program	Dr Paul Lacante Av. de Finlande, 4 1420 Braine l'Alleud Belgium Tel: +3223527592 Email: paul.lacante@bms.com
Modalities for the disposal	Unused or expired medication will be destroyed at the hospital pharmacy according to local regulations.
The information for registration of suspected unexpected serious adverse reactions	The most common side effects of nivolumab are: • Fatigue • Skin reactions: including rash, itching, hives, redness, and dry skin • Diarrhea • Nausea • Abdominal pain • Decreased appetite • Low red blood cells • Fever • Joint pain or stiffness The treating physician should report any adverse event to the below contact person. <u>Adverse Events Reporting Contact:</u>

	Mrs. Patricia VANDAMME, Head of Country Pharmacovigilance Belgium Avenue de Finlande, 4 1420 Braine-l'Alleud Fax number: 02 352 75 66 Email: safety_belgium@bms.com