Summary of Product Specification

1. Name of the medicinal product

Niraparix Capsule 100 mg hard capsules

2. Qualitative and quantitative composition

Each hard capsule contains Niraparib Tosylate Monohydrate equivalent to 100 mg Niraparib.

Excipients with known effect

Each hard capsule contains 254.5 mg of lactose monohydrate.

Each hard-capsule shell also contains the coloring agent tartrazine.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Hard capsule

A White to off-white colored powder is encapsulated into Hard Gelatin capsule shell, Size # 1. (Yellow OP Body, Green OP cap)

4. Clinical particulars

4.1 Therapeutic indications

Niraparib is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

4.2 Posology and method of administration

Treatment with Niraparib should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Posology

The dose is three 100 mg hard capsules once daily, equivalent to a total daily dose of 300 mg.

Patients should be encouraged to take their dose at approximately the same time each day. Bedtime administration may be a potential method for managing nausea.

It is recommended that treatment should be continued until disease progression.

Missing dose

If patients miss a dose, they should take their next dose at its regularly scheduled time.

Dose adjustments for adverse reactions

Recommendations for the management of adverse reactions are provided in Table 1. In general, it is recommended to first interrupt the treatment (but no longer than 28 consecutive days) to allow the patient to recover from the adverse reaction and then restart at the same dose. In the case that the adverse reaction recurs, it is recommended to reduce the dose. If adverse reactions persist beyond a 28-day dose interruption, it is recommended that Niraparib be discontinued. If adverse reactions are not manageable with this strategy of dose interruption and reduction, it is recommended that Niraparib be discontinued.

Dose reductions may be implemented based on adverse reactions. The recommended dose reductions are first from three hard capsules daily (300 mg) to two hard capsules daily (200 mg). If further dose reduction is needed, a second dose reduction from two hard capsules daily (200 mg) to one capsule daily (100 mg) may be implemented.

Patients with low body weight

Approximately 25 % of patients in the NOVA study weighed less than 58 kg, and approximately 25 % of patients weighed more than 77 kg. The incidence of Grade 3 or 4 ADRs was greater among low body weight patients (78%) than high body weight patients (53 %). Only 13 % of low body weight patients remained at a dose of 300 mg beyond Cycle 3. A starting dose of 200 mg for patients weighing less than 58 kg may be considered.

Elderly

No dose adjustment is necessary for elderly patients (≥ 65 years). There are limited clinical data in patients aged 75 or over.

Renal impairment

No dose adjustment is necessary for patients with mild to moderate renal impairment. There are no data in patients with severe renal impairment or end stage renal disease undergoing haemodialysis; use with caution in these patients.

Hepatic impairment

No dose adjustment is needed in patients with mild to moderate hepatic impairment. There are no data in patients with severe hepatic impairment; use with caution in these patients.

Patients with ECOG performance status 2 to 4

Clinical data are not available in patients with ECOG performance status 2 to 4.

Pediatric population

The safety and efficacy of niraparib in children and adolescents below 18 years of age have not yet been established. No data are available.

Method of administration

Oral use. The capsules should be swallowed whole with water. The capsules should not be chewed or crushed.

Niraparib can be taken without regard to meals.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Breast-feeding.

4.4 Special warnings and precautions for use

Hematologic adverse reactions

In the NOVA study, patients eligible for Niraparib therapy had the following baseline haematologic parameters: absolute neutrophil count (ANC) ≥ 1,500 cells/μL; platelets ≥ 100,000 cells/μL and haemoglobin ≥ 9 g/dL prior to therapy. Haematologic adverse reactions (thrombocytopenia, anaemia, neutropenia) have been reported in patients treated with Niraparib. In the NOVA study, 48 of 367 (13 %) of patients experienced bleeding with concurrent thrombocytopenia; all bleeding events concurrent with thrombocytopenia were Grade 1 or 2 in severity except for one event of Grade 3 petechiae and haematoma observed concurrently with a serious adverse event of pancytopenia. Thrombocytopenia occurred more commonly in patients whose baseline platelet count was less than 180 × 109/L. Approximately 76 % of patients with lower baseline platelets (< 180 × 109/L) who received Niraparib experienced thrombocytopenia of any grade, and 45 % of the patients experienced Grade 3/4 thrombocytopenia. Pancytopenia has been observed in < 1 % of patients receiving niraparib. If a patient develops severe persistent haematologic toxicity including pancytopenia that does not resolve within 28 days following interruption, Niraparib should be discontinued.

Testing complete blood counts weekly for the first month, followed by monthly monitoring for the next 10 months of treatment and periodically after this time is recommended to monitor for clinically significant changes in any hematologic parameter during treatment.

If a patient develops severe persistent hematologic toxicity that does not resolve within 28 days following interruption, Niraparib should be discontinued.

Due to the risk of thrombocytopenia, anticoagulants and medicinal products known to reduce the thrombocyte count should be used with caution.

Myelodysplastic syndrome/acute myeloid leukemia

Myelodysplastic syndrome/acute myeloid leukemia (MDS/AML), including cases with fatal outcome, have been reported in a small number of patients who received Niraparib or placebo. In the pivotal Phase 3 international trial (ENGOT-OV16), the incidence of MDS/AML in patients who received niraparib (1.4 %) was similar to that in patients who received placebo (1.1 %). Overall, MDS/AML has been reported in 7 out of 751 (0.9 %) patients treated with Niraparib in clinical studies.

The duration of Niraparib treatment in patients prior to developing MDS/AML varied from 1 month to > 2 years. The cases were typical of secondary, cancer therapy-related MDS/AML. All patients had received multiple platinum-containing chemotherapy regimens and many had also received other DNA damaging agents and radiotherapy. Some of the patients had a history of bone marrow dysplasia.

If MDS and/or AML are confirmed while on treatment with Niraparib, treatment should be discontinued and the patient treated appropriately.

Hypertension, including hypertensive crisis

Hypertension, including hypertensive crisis, has been reported with the use of Niraparib. Pre-existing hypertension should be adequately controlled before starting Niraparib treatment. Blood pressure should be monitored monthly for the first year and periodically thereafter during treatment with Niraparib.

Hypertension should be medically managed with antihypertensive medicinal products as well as adjustment of the Niraparib dose, if necessary. In the clinical program, blood pressure measurements were obtained on Day 1 of each 28-day cycle while the patient remained on Niraparib. In most cases, hypertension was controlled adequately using standard antihypertensive treatment with or without

Niraparib dose adjustment. Niraparib should be discontinued in case of hypertensive crisis or if medically significant hypertension cannot be adequately controlled with antihypertensive therapy.

Pregnancy/contraception

Niraparib should not be used during pregnancy or in women of childbearing potential not willing to use reliable contraception during therapy and for 1 month after receiving the last dose of Niraparib. A pregnancy test should be performed on all women of childbearing potential prior to treatment.

Lactose

Niraparib hard capsules contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Tartrazine

This medicinal product contains tartrazine (E 102), which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

The combination of niraparib with vaccines or immunosuppressant agents has not been studied. The data on niraparib in combination with cytotoxic medicinal products are limited. Therefore, caution should be taken if niraparib is used in combination with vaccines, immunosuppressant agents or with other cytotoxic medicinal products.

Pharmacokinetic interactions

Effect of other medicinal products on niraparib

Niraparib as a substrate of CYPs (CYP1A2 and CYP3A4)

Niraparib is a substrate of carboxylesterases (CEs) and UDP-glucuronosyltransferases (UGTs) in vivo. Oxidative metabolism of niraparib is minimal in vivo. No dose adjustment for Niraparib is required when administered concomitantly with medicinal products known to inhibit (e.g. itraconazole, ritonavir, and clarithromycin) or induce CYP enzymes (e.g. rifampin, carbamazepine, and phenytoin).

Niraparib as a substrate of efflux transporters (P-gp, BCRP, and MATE1/2)

Niraparib is a substrate of P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP). However, due to its high permeability and bioavailability, the risk of clinically relevant interactions with medicinal products that inhibit these transporters is unlikely. Therefore, no dose adjustment for Niraparib is required when administered concomitantly with medicinal products known to inhibit P-gp (e.g. amiodarone, verapamil) or BCRP (e.g. osimertinib, velpatasvir, and eltrombopag).

Niraparib is not a substrate of bile salt export pump (BSEP). The major primary metabolite M1 is not a substrate of P-gp, BCRP, or BSEP. Niraparib is not a substrate of MATE 1 or 2, while M1 is a substrate of both.

Niraparib as a substrate of hepatic uptake transporters (OATP1B1, OATP1B3, and OCT1)

Neither niraparib nor M1 is a substrate of organic anion transport polypeptide 1B1 (OATP1B1), 1B3 (OATP1B3), or organic cation transporter 1 (OCT1). No dose adjustment for Niraparib is required when administered concomitantly with medicinal products known to inhibit OATP1B1 or 1B3 (e.g. gemfibrozil, ritonavir), or OCT1 (e.g. dolutegravir) uptake transporters.

Niraparib as a substrate of renal uptake transporters (OAT1, OAT3, and OCT2)

Neither niraparib nor M1 is a substrate of organic anion transporter 1 (OAT1), 3 (OAT3), and organic cation transporter 2 (OCT2). No dose adjustment for Niraparib is required when administered concomitantly with medicinal products known to inhibit OAT1 (e.g. probenecid) or OAT3 (e.g. probenecid, diclofenac), or OCT2 (e.g. cimetidine, quinidine) uptake transporters.

Effect of niraparib on other medicinal products

Inhibition of CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4)

Neither niraparib nor M1 is an inhibitor of any active substance-metabolising CYP enzymes, namely CYP1A1/2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5.

Even though inhibition of CYP3A4 in the liver is not expected, the potential to inhibit CYP3A4 at the intestinal level has not been established at relevant niraparib concentrations. Therefore, caution is recommended when niraparib is combined with active substances the metabolism of which is CYP3A4-dependent and, notably, those having a narrow therapeutic range (e.g. ciclosporin, tacrolimus, alfentanil, ergotamine, pimozide, quetiapine, and halofantrine).

Induction of CYPs (CYP1A2 and CYP3A4)

Neither niraparib nor M1 is a CYP3A4 inducer in vitro. In vitro, niraparib weakly induces CYP1A2 at high concentrations and the clinical relevance of this effect would not be completely ruled out. M1 is not a CYP1A2 inducer. Therefore, caution is recommended when niraparib is combined with active substances the metabolism of which is CYP1A2-dependent and, notably, those having a narrow therapeutic range (e.g. clozapine, theophylline, and ropinirole).

Inhibition of efflux transporters (P-gp, BCRP, BSEP, and MATE1/2)

Niraparib is not an inhibitor of BSEP. In vitro, niraparib inhibits P-gp very weakly and BCRP with an IC50 = 161 µM and 5.8 µM, respectively. Therefore, a clinically meaningful interaction related to an inhibition of these efflux transporters although unlikely, cannot be excluded. Caution is then recommended when niraparib is combined with substrates of BCRP (irinotecan, rosuvastatin, simvastatin, atorvastatin, and methotrexate).

Niraparib is an inhibitor of MATE1 and -2 with IC50 of 0.18 µM and ≤ 0.14 µM, respectively. Increased plasma concentrations of co-administered medicinal products that are substrates of these transporters (e.g. metformin) cannot be excluded.

The major primary metabolite M1 does not appear to be an inhibitor of P-gp, BCRP, BSEP, or MATE1/2.

Inhibition of hepatic uptake transporters (OATP1B1, OATP1B3, and OCT1)

Neither niraparib nor M1 is an inhibitor of organic anion transport polypeptide 1B1 (OATP1B1) or 1B3 (OATP1B3).

In vitro, niraparib weakly inhibits the organic cation transporter 1 (OCT1) with an IC50 = 34.4 µM. Caution is recommended when niraparib is combined with active substances that undergo an uptake transport by OCT1 such as metformin.

Inhibition of renal uptake transporters (OAT1, OAT3, and OCT2)

Neither niraparib nor M1 inhibits organic anion transporter 1 (OAT1), 3 (OAT3), and organic cation transporter 2 (OCT2).

All clinical studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in females

Women of childbearing potential should not become pregnant while on treatment and should not be pregnant at the beginning of treatment. A pregnancy test

should be performed on all women of childbearing potential prior to treatment. Women of childbearing potential must use effective contraception during therapy and for 1 month after receiving the last dose of Niraparib.

Pregnancy

There are no or limited amount of data from the use of niraparib in pregnant women. Animal reproductive and developmental toxicity studies have not been conducted. However, based on its mechanism of action, niraparib could cause embryonic or foetal harm, including embryo-lethal and teratogenic effects, when administered to a pregnant woman. Niraparib should not be used during pregnancy.

Breast-feeding

It is unknown whether niraparib or its metabolites are excreted in human milk. Breast-feeding is contraindicated during administration of Niraparib and for 1 month after receiving the last dose.

Fertility

There are no clinical data on fertility. A reversible reduction of spermatogenesis was observed in rats and dogs.

4.7 Effects on ability to drive and use machines

Niraparib has moderate influence on the ability to drive or use machines. Patients who take Niraparib may experience asthenia, fatigue and dizziness. Patients who experience these symptoms should observe caution when driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

In the pivotal ENGOT-OV16 study, adverse reactions (ADRs) occurring ≥ 10 % of patients receiving Niraparib monotherapy were nausea, thrombocytopenia, fatigue/asthenia, anemia, constipation, vomiting, abdominal pain, neutropenia, insomnia, headache, decreased appetite, nasopharyngitis, diarrhea, dyspnea, hypertension, dyspepsia, back pain, dizziness, cough, urinary tract infection, arthralgia, palpitations, and dysgeusia.

The most common serious adverse reactions > 1 % (treatment-emergent frequencies) were thrombocytopenia and anemia.

Description of selected adverse reactions

Hematologic adverse reactions (thrombocytopenia, anemia, neutropenia) including clinical diagnoses and/or laboratory findings generally occurred early during niraparib treatment with the incidence decreasing over time.

Thrombocytopenia

Approximately 60 % of patients receiving Niraparib experienced thrombocytopenia of any grade, and 34 % of patients experienced Grade 3/4 thrombocytopenia. In patients with baseline platelet count less than 180 × 109/L, thrombocytopenia of any grade and Grade 3/4 occurred in 76 % and 45 % of the patients, respectively. The median time to onset of thrombocytopenia regardless of grade and Grade 3/4 thrombocytopenia was 22 and 23 days, respectively. The rate of new incidences of thrombocytopenia after intensive dose modifications were performed during the first two months of treatment from Cycle 4 was 1.2 %. The median duration of thrombocytopenia events of any grade was 23 days, and the median duration of Grade 3/4 thrombocytopenia was 10 days. Patients treated with Niraparib who develop thrombocytopenia might have an increased risk of hemorrhage. In the clinical programme, thrombocytopenia was managed with laboratory monitoring, dose modification and platelet transfusion where appropriate. Discontinuation due to thrombocytopenia events (thrombocytopenia and platelet count decreased) occurred in approximately 3 % of the patients.

Anaemia

Approximately 50 % of patients experienced anaemia of any grade, and 25 % experienced Grade 3/4 anaemia. The median time to onset of anaemia of any grade was 42 days, and 85 days for Grade 3/4 events. The median duration of anaemia of any grade was 63 days, and 8 days for Grade 3/4 events. Anaemia of any grade might persist during Niraparib treatment. In the clinical programme, anaemia was managed with laboratory monitoring, dose modification, and where appropriate with red blood cell transfusions. Discontinuation due to anaemia occurred in 1 % of patients.

Neutropenia

Approximately 30 % of patients receiving Niraparib experienced neutropenia of any grade, and 20 % of patients experienced Grade 3/4 neutropenia. The median time to onset of neutropenia of any grade was 27 days, and 29 days for Grade 3/4 events. The median duration of neutropenia of any grade was 26 days, and 13 days for Grade 3/4 events. In the clinical program, neutropenia was managed with laboratory monitoring and dose modifications. In addition, Granulocyte-Colony Stimulating Factor (G-CSF) was administered to approximately 6 % of

patients treated with niraparib as concomitant therapy for neutropenia. Discontinuation due to neutropenia events occurred in 2 % of patients.

Hypertension

Hypertension, including hypertensive crisis, has been reported with Niraparib therapy. Hypertension of any grade occurred in 19.3 % of patients treated with Niraparib. Grade 3/4 hypertension occurred in 8.2 % of patients. In the clinical program, hypertension was readily managed with anti-hypertensive medicinal products. Discontinuation due to hypertension occurred in < 1 % of patients.

Pediatric population

No studies have been conducted in pediatric patients.

4.9 Overdose

There is no specific treatment in the event of Niraparib overdose, and symptoms of overdose are not established. In the event of an overdose, physicians should follow general supportive measures and should treat symptomatically.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antineoplastic agents.

Mechanism of action and pharmacodynamic effects

Niraparib is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, PARP-1 and PARP-2, which play a role in DNA repair. In vitro studies have shown that niraparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes resulting in DNA damage, apoptosis and cell death. Increased niraparib-induced cytotoxicity was observed in tumour cell lines with or without deficiencies in the BReast CAncer (BRCA) 1 and 2 tumour suppressor genes. In orthotopic high-grade serous ovarian cancer patient-derived xenograft tumours (PDX) grown in mice, niraparib has been shown to reduce tumour growth in BRCA 1 and 2 mutant, BRCA wild-type but homologous recombination (HR) deficient, and in tumours that are BRCA wild-type and without detectable HR deficiency.

5.2 Pharmacokinetic properties

Absorption

Following a single-dose administration of 300 mg niraparib under fasting conditions, niraparib was measurable in plasma within 30 minutes and the mean peak plasma concentration (C_{max}) for niraparib was reached in about 3 hours [804 ng/mL (% CV:50.2 %)]. Following multiple oral doses of niraparib

from 30 mg to 400 mg once daily, accumulation of niraparib was approximately 2 to 3 folds.

The systemic exposures (C_{max} and AUC) to niraparib increased in a dose-proportional manner when the dose of niraparib increased from 30 mg to 400 mg. The absolute bioavailability of niraparib is approximately 73 %, indicating minimal first pass effect.

A concomitant high-fat meal did not significantly affect the pharmacokinetics of niraparib after administration of 300 mg of niraparib.

Distribution

Niraparib was moderately protein bound in human plasma (83.0 %), mainly with serum albumin. In a population pharmacokinetic analysis of niraparib, the Vd/F was 1,074 L in cancer patients, indicating extensive tissue distribution of niraparib.

Biotransformation

Niraparib is metabolized primarily by carboxylesterases (CEs) to form a major inactive metabolite, M1. In a mass balance study, M1 and M10 (the subsequently formed M1 glucuronides) were the major circulating metabolites.

Elimination

Following a single oral 300-mg dose of niraparib, the mean terminal half-life (t½) of niraparib ranged from 48 to 51 hours (approximately 2 days). In a population pharmacokinetic analysis, the apparent total clearance (CL/F) of niraparib was 16.2 L/h in cancer patients.

Niraparib is eliminated primarily through the hepatobiliary and renal routes. Following an oral administration of a single 300-mg dose of [14C]-niraparib, on average 86.2 % (range 71 % to 91 %) of the dose was recovered in urine and feces over 21 days. Radioactive recovery in the urine accounted for 47.5 % (range 33.4 % to 60.2 %) and in the feces for 38.8 % (range 28.3 % to 47.0 %) of the dose. In pooled samples collected over 6 days, 40.0 % of the dose was recovered in the urine primarily as metabolites and 31.6 % of the dose was recovered in the feces primarily as unchanged niraparib.

Special populations

Renal impairment

In the population pharmacokinetic analysis of data from clinical studies in patients, pre-existing mild (CLCr < 90 - ≥ 60 ml/min) and moderate (CLCr < 60 - ≥ 30 mL/min) renal impairment did not influence the clearance of niraparib.

No patients with pre-existing severe renal impairment or end-stage renal disease undergoing hemodialysis were identified in clinical studies.

Hepatic impairment

In the population pharmacokinetic analysis of data from clinical studies in patients, pre-existing mild and moderate hepatic impairment did not influence the clearance of niraparib. The pharmacokinetics of niraparib have not been assessed in patients with severe hepatic impairment

Age, weight and race

Population pharmacokinetic analyses indicated that age, weight and race had no significant impact on the pharmacokinetics of niraparib.

Pediatric population

No studies have been conducted to investigate the pharmacokinetics of niraparib in pediatric patients.

5.3 Preclinical safety data

Secondary pharmacology

In vitro, niraparib inhibited the dopamine transporter DAT at concentration levels below human exposure levels. In mice, single doses of niraparib increased intracellular levels of dopamine and metabolites in cortex. Reduced locomotor activity was seen in one of two single dose studies in mice. The clinical relevance of these findings is not known. No effect on behavioral and/or neurological parameters have been observed in repeat-dose toxicity studies in rats and dogs at estimated CNS exposure levels similar to or below expected therapeutic exposure levels.

Repeat-dose toxicity

In repeat-dose oral toxicity studies, niraparib was administered daily for up to 3 months' duration in rats and dogs. The major primary target organ for toxicity in both species was the bone marrow, with associated changes in peripheral hematology parameters. Additionally, decreased spermatogenesis was seen in both species. These findings occurred at exposure levels below those seen clinically, and were largely reversible within 4 weeks of cessation of dosing.

Genotoxicity

Niraparib was not mutagenic in a bacterial reverse mutation assay (Ames) test but was clastogenic in an in vitro mammalian chromosomal aberration assay and in an in vivo rat bone marrow micronucleus assay. This clastogenicity is

consistent with genomic instability resulting from the primary pharmacology of niraparib and indicates potential for genotoxicity in humans.

Reproductive toxicology

Reproductive and developmental toxicity studies have not been conducted with niraparib.

Carcinogenicity

Carcinogenicity studies have not been conducted with niraparib.

6. Pharmaceutical particulars

6.1 List of excipients

Capsule content

Sodium Starch Glycolate (Primojel)

Polacrilin Potassium (Kyron-T314)

Sodium Lauryl Sulphate

Magnesium Stearate

Colloidal Anhydrous Silica (Aerosil 200)

Mannitol (DC Grade)

Microcrystalline Cellulose

Empty hard Gelatin Capsule Shell, size # 1 (Yellow OP Body and Green OP cap)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30 °C.

6.5 Nature and contents of container

Primary Packaging: HDPE pot

Pack size: 1 × 90’s capsules in Box

Secondary Packaging: Paper board carton

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorization holder

Beacon Medicare Limited

9/B/2 Toyenbee Circular Road

Motijheel, Dhaka

Bangladesh -1223

8. Marketing authorization number(s)

H2022/CTD8541/18661

9. Date of first authorization/renewal of the authorization

2022 August 02

10. Date of revision of the text

07-08-2024