DORIPENEM

DROFEPEN

500 mg Powder for Intravenous Infusion

ANTIBACTERIAL (CARBAPENEM)

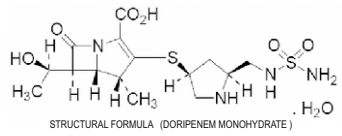
℞

FORMULATION
Each vial contains:
Doripenem Monohydrate
equivalent to Doripenem ..... 500 mg

PHARMACOTHERAPEUTIC CLASS: Carbapenems (ultra-broad spectrum antibiotic)

DOSAGE FORM
Powder for Intravenous Infusion.

PRODUCT DESCRIPTION
White to yellow colour powder
Drofepen contains doripenem monohydrate, which is a synthetic broad-spectrum carbapenem antibiotic structurally related to beta-lactarn antibiotics. The chemical name for doripenem monohydrate is (4R, 5S, 6S)-3-[((3S, 5S)-5-[[(aminosulfonyl) amino] methyl]-3-pyrrolidinyl)thio]-6-[(1 R)-1- hydroxyethyl]-4-methyl-7 -oxo-1-azabicyclo[3.2 .0)hept-2-ene-2- carboxylic acid monohydrate. Its molecular formula is $C_{15}\ H_{24}\ N_4\ O_5\ S_2 \cdot H_2O$ and its molecular weight is 438.52. The chemical structure doripenem monohydrate is given below:



STRUCTURAL FORMULA (DORIPENEM MONOHYDRATE)

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES
Pharmacodynamics
Similar to other beta-lactam antimicrobial agents, the time that unbound plasma concentration of doripenem exceeds the MIC of the infecting organism has been shown to best correlate with efficacy in animal models of infection. However the pharmacokinetic & pharmacodynamic relationship for doripenem has not been evaluated in patients. No significant effect on QTc interval was detected at peak plasma concentration or at any other time in healthy subjects receiving doripenem 500 mg IV every 8 hrs x 4 doses, doripenem 1g IV every 8 hrs x 4 doses, placebo and a single oral dose positive control in a randomized, positive- and placebo-controlled crossover study.

Mechanism of action
Doripenem belongs to the carbapenem class of antimicrobials. Doripenem exerts its bactericidal activity by inhibiting bacterial cell wall biosynthesis. Doripenem inactivates multiple essential penicillin-binding proteins (PBPs) resulting in inhibition of cell wall synthesis with subsequent cell death. In *E. Coli and P. aeruginosa*, doripenem binds to PBP 2, which is involved in the maintenance of cell shape, as well as to PBPs 3 and 4.

Antibacterial spectrum
Doripenem has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections.
Facultative gram-negative microorganisms
Klebsiella pneumoniae
Acinetobacter baumannii
Escherichia coli
Proteus mirabilis
Pseudomonas aeruginosa
Facultative gram-positive microorganisms
Streptococcus constellatus
Streptococcus intermedius
Anaerobic microorganisms
Bacteroides caccae
Bacteroides fragilis
Bacteroides thetaiotaomicron
Bacteroides uniformis
Bacteroides vulgatus
Peptostreptococcus micros
At least 90 percent of the following microorganisms exhibit an *in vitro* minimal inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for doripenem. The safety and efficacy of doripenem in treating clinical infections due to these microorganisms has not been established in adequate and well controlled clinical trials.
Facultative gram-positive microorganisms.
Staphylococcus aureus (methicillin-susceptible isolates only)
Streptococcus agalactiae
Streptococcus pyogenes
Facultative gram-negative microorganisms
Citrobacter freundii
Enterobacter cloacae
Enterobacter aerogenes
Klebsiella oxytoca
Morganella morganii
Serratia marcescens

Mechanism(s) of resistance
Bacterial resistance mechanisms that affect doripenem include drug inactivation by carbapenem-hydrolyzing enzymes, mutant or acquired PBPs, decreased outer membrane permeability and active efflux. Doripenem is stable to hydrolysis by most β-lactamases including penicillinases and cephalosporinases produced by gram-positive and gram-negative bacteria, with the exception of carbapenem hydrolyzing β-lactamases. Although cross-resistance may occur, some isolates resistant to other carbapenems may be susceptible to doripenem.

Pharmacokinetics
Mean (SD) plasma C_{max} and $AUC_{0\text{-}\infty}$ value of doripenem were 23.0 (6.6) µg/mL and 36.3 (8.8) µg•hr/mL, respectively following a single 1-hour intravenous infusion of a 500 mg dose of doripenem to healthy subjects. The pharmacokinetics of doripenem (C_{max} and AUC) are linear over a dose range of 500 mg to 1g when intravenously range of 500 mg to 1g administered every 8 hours for 7 to 10 days in subjects with normal renal function. The average binding of doripenem to plasma proteins is approximately 8.1 % and is independent of plasma drug concentrations. The median (range) volume of distribution at steady state in healthy subjects is 16.8 L (8.09-55.5 L), similar to extracellular fluid volume (18.2 L).

Doripenem penetrates into several body fluids and tissues, including those at the site of infection for the approved indications, Doripenem concentrations in peritoneal and retroperitoneal fluid either match or exceed those required to inhibit most susceptible bacteria; however, the clinical relevance of this finding has not been established. Concentrations achieved in selected tissues and fluids following administration of doripenem are shown in table below:

Table: Doripenem Concentrations in Selected Tissues and Fluids

Tissue or Fluid	Dose (mg)	Infusion Duration(h)	Number of Sample or Subject*	Sampling Period[b]	Concentration Range (mcg/mL or mcg/g)	Tissue or Fluid to Plasma Concentration (%) Mean (Range)
Retroperitoneal Fluid	250	0.5	9	30-90 min[d]	3.15-52.4	Range: 4.1(0.5-9.7) at 0.25 h to 990 (173-2609) at 2.5 h
	500	0.5	4	90 min[d]	9.53-13.9	Range: 3.3(0.0-8.1) at 0.25 h to 516 (311-842) at 6.5 h
Peritoneal exudate	250	0.5	5	20-150 min	BQL-1.87[e]	8.02(0.00-44.4)
Bile	250	0.5	10	20-125 min	BQL-15.4[f]	117 (0.00-611)
Urine	500	1	110	0-4 hr	601(BQLf-3360)[g]	--
	500	1	110	4-8 hr	49.7(BQLf-365)[g]	--

b = Time from start of infusion; c = Serial samples were collected; maximum concentrations reported;
d =t_{max} range; e =BQL(Below Quantifiable Limit) in 6 subjects; f =BQL in 1 subject; g = Median (range)

Metabolism of doripenem to a microbiologically inactive ring opened metabolite (doripenem-M1) occurs primarily via dehydropeptidase-I. The mean (SD) plasma doripenem-M1-to- doripenem AUC ratio following single 500 mg and 1 g doses in healthy subjects is 18% (7.2%).

In pooled human liver microsomes, no *in vitro* metabolism of doripenem could be detected, indicating that doripenem is not a substrate for hepatic CYP450 enzymes. Doripenem is primarily eliminated unchanged by the kidneys. The mean plasma terminal elimination half-life of doripenem in healthy non-elderly adults is approximately 1 hr and mean (SD) plasma clearance is 15.9 (5.3) L/hr. Mean (SD) renal clearance is 10.8 (3.5) L/hr.

The magnitude of this value, coupled with the significant decrease in the elimination of doripenem with concomitant probenecid administration, suggests that doripenem undergoes both glomerular filtration and active tubular secretion. In healthy adults given a single 500 mg dose of doripenem, a mean of 70% and 15% of the dose was recovered in urine as unchanged drug and the ring-opened metabolite, respectively, within 48 hrs. Following the administration of a single 500 mg dose of radiolabeled doripenem to healthy adults, less than 1% of the total radioactivity was recovered in feces after one week.

Pharmacokinetics in Special Populations
P*atients with renal impairment:* Following a single 500 mg dose of doripenem for injection, the mean AUC of doripenem in subjects with mild Creatinine Clearance (CrCl 50-79,mL/min), moderate (CrCl 31-50 mL/min), and severe renal impairment (CrCl ≤ 30 mL/min) was 1.6-, 2.8-, and 5.1-times that of age-matched healthy subjects with normal renal function (CrCl ≥ 80 mL/min), respectively. Dosage adjustment is necessary in patients with moderate and severe renal impairment.

A single 500 mg dose of doripenem was administered to subjects with end stage renal disease (ESRD) either one hour prior to or one hour after hemodialysis (HD). The mean doripenem AUC following the post-HD infusion was 7.8-times that of healthy subjects with normal renal function. The mean total recovery of doripenem and doripenem-M1 in the dialysate following a 4-hour HD session was 231 mg and 28 mg, respectively, or a total of 259 mg (52% of the- dose). There is insufficient information to make dose adjustment recommendations in patients on hemodialysis.

Patients with hepatic impairment: The pharmacokinetics of doripenem in patients with hepatic impairment have not been established as doripenem does not appear to undergo hepatic metabolism, the pharmacokinetics of doripenem are not expected to be affected by hepatic impairment.

Geriatric patients: The impact of age on the pharmacokinetics of doripenem was evaluated in healthy male and female subjects ≥ 66 years of age. Mean doripenem AUC was 49% higher in elderly adults relative to non-elderly adults. This difference in exposure was mainly attributed to age-related changes in creatinine clearance. No dosage adjustment is recommended for elderly patients with normal (for their age) renal function.

Gender: The effect of gender on the pharmacokinetics of doripenem was evaluated in healthy male and female subjects. Doripenem C_{max} and AUC were similar between males and females. No dose adjustment is recommended based on gender.

Race: The effect of race on doripenem pharmacokinetics was examined using a population pharmacokinetic analysis of data from phase 1 and 2 studies. Compared to Caucasians, mean doripenem clearance was 14% greater in Hispanic / Latino subjects whereas no difference in clearance was observed for African Americans. Doripenem clearance in Japanese studies is similar to what has been observed in Western populations. No dosage adjustment is recommended based on race.

INDICATIONS
Doripenem for injection is indicated for the treatment of infections caused by susceptible microorganisms in the following conditions: Nosocomial pneumonia (Including ventilator associated pneumonia), Complicated intra-abdominal infection and Complicated urinary tract infection including pyelonephritis.

DOSAGE AND ADMINISTRATION
Recommended Dosage
The recommended dosage of Doripenem is 500 mg administered every 8 hours by intravenous infusion over one hour in patients ≥18 years of age. The recommended dosage and administration by infection is described in Table 1:

Table 1: Dosage of Doripenem by Infection

Infection	Dosage	Frequency	Infusion Time (hours)	Duration
Complicated intra-abdominal infection	500 mg	q8h	1	5–14 days*
Complicated UTI, including pyelonephritis	500 mg	q8h	1	10 days*†

* Duration includes a possible switch to an appropriate oral therapy, after at least 3 days of parenteral therapy, once clinical improvement has been demonstrated.
† Duration can be extended up to 14 days for patients with concurrent bacteremia.

Patients with Renal Impairment
Table 2: Dosage of Doripenem in Patients with Renal Impairment

Estimated CrCl (mL/min)	Recommended Dosage Regimen of Doripenem
> 50	No dosage adjustment necessary
⩾ 30 to ⩽ 50	250 mg intravenously (over 1 hour) every 8 hours
> 10 to < 30	250 mg intravenously (over 1 hour) every 12 hours

The following formula may be used to estimate CrCl. The serum creatinine used in the formula should represent a steady state of renal function.

$$\text{Males: Creatinine clearance (mL/min)} = \frac{\text{weight (kg)} \times (140 - \text{age in years})}{72 \times \text{serum creatinine (mg/dL)}}$$

$$\text{Females: Creatinine clearance (mL/min)} = 0.85 \times \text{value calculated for males}$$

Doripenem is hemodialyzable; however, there is insufficient information to make dose adjustment recommendations in patients on hemodialysis.

Direction for Reconstitution: Doripenem does not contain a bacteriostatic preservative. Aseptic technique must be followed in preparation of the infusion solution.
Preparation of 500 mg Doripenem dose using the 500 mg vial

- Constitute the 500 mg vial with 10 mL of sterile water for injection or 0.9% sodium chloride injection (normal saline) and gently shake to form a suspension. The resultant concentration is approximately 50 mg/mL. CAUTION: THE CONSTITUTED SUSPENSION IS NOT FOR DIRECT INJECTION.
- Withdraw the suspension using a syringe with a 21 gauge needle and add it to an infusion bag containing 100 mL of normal saline or 5% dextrose; gently shake until clear. The final infusion solution concentration is approximately 4.5 mg/mL.

Preparation of 250 mg Doripenem dose using the 250 mg vial

- Constitute the 250 mg vial with 10 mL of sterile water for injection or 0.9% sodium chloride injection (normal saline) and gently shake to form a suspension. The resultant concentration is approximately 25 mg/mL. CAUTION: THE CONSTITUTED SUSPENSION IS NOT FOR DIRECT INJECTION.
- Withdraw the suspension using a syringe with a 21 gauge needle and add it to an infusion bag containing either 50 or 100 mL of normal saline or 5% dextrose; gently shake until clear. The final infusion solution concentration is approximately 4.2 mg/mL (50 mL infusion bag) or approximately 2.3 mg/mL (100 mL infusion bag).

Preparation of 250 mg Doripenem dose using the 500 mg vial

- Constitute the 500 mg vial with 10 mL of sterile water for injection or 0.9% sodium chloride injection (normal saline) and gently shake to form a suspension. The resultant concentration is approximately 50 mg/mL. CAUTION: THE CONSTITUTED SUSPENSION IS NOT FOR DIRECT INJECTION.
- Withdraw the suspension using a syringe with a 21 gauge needle and add it to an infusion bag containing 100 mL of normal saline or 5% dextrose; gently shake until clear.
- Remove 55 mL of this solution from the bag and discard.
- Infuse the remaining solution, which contains 250 mg (approximately 4.5 mg/mL).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to use whenever solution and container permit. Doripenem infusions range from clear, colorless solutions to solutions that are clear and slightly yellow. Variations in color within this range do not affect the potency of the product.

Storage and Stability Times of **Doripenem** Infusion Solutions		
Infusion solution	Stability Time (includes storage and infusion time)	
(Infusion prepared in)	At Room Temp.	At 2-8°C (Refrigeration)
Normal saline	12 hours	72 hours
5% Dextrose Injection	4 hours	24 hours

Size : 200 x 320 mm
54 gsm Maplitho paper

CONTRAINDICATION
Doripenem for injection is contraindicated in patients with known serious hypersensitivity to doripenem or to other drugs in the same class or in patients who have demonstrated anaphylactic reaction to ß-lactams.

WARNINGS
Hypersensitivity reactions: Serious and occasionally fatal hypersensitivity (anaphylactic) and serious skin reactions have been reported in patients receiving beta-lactam antibiotics. These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. Before therapy with doripenem is instituted, careful inquiry should be made to determine whether the patient has had a previous hypersensitivity reaction to other carbapenems, cephalosporins, penicillins or other allergens. If this product is to be given to penicillin- or other ß-lactam -allergic patient, caution should be exercised because cross- hyperreactivity among ß-lactam antibiotics has been clearly documented. If an allergic reaction to doripenem occurs, discontinue the drug. Serious acute hypersensitivity (anaphylactic) reactions require emergency treatment with epinephrine and other emergency measures, including oxygen, IV fluids, IV antihistamines, corticosteroids , pressor amines and airway management, as clinically indicated.
Clostridium difficile-associated diarrhea
Clostridium difficile-associated diarrhea (CDAD) has been reported with nearly all antibacterial agents and may range in severity from mild diarrhea to fatal colitis.
Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of *C. difficile.*
C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. *difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.
If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS
General:
Interaction with sodium valproate:
CARBAPENEMS may reduce serum valproic acid concentrations to subtherapeutic levels, resulting in loss of seizure control. Serum valproic acid concentrations should be monitored frequently after initiating carbapenem therapy. Alternative antibacterial or anticonvulsant therapy should be considered if serum valproic acid cannot be maintained in the therapeutic range or seizures occur.

Development of drug-resistant bacteria
Prescribing doripenem in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increase the risk of the development of drug resistant bacteria.

Pneumonitis with inhalational use
When doripenem has been used investigationally via inhalation, pneumonitis has occurred. Doripenem for Injection should not be administered this route.

Geriatrics
Of the total number of subjects in clinical studies, 28% were 65 and over, while 12% were 75 and over. Clinical cure rates in complicated intra-abdominal and complicated urinary tract infections where slightly lower in patients ≥ 65 years of age and also in the subgroup of patients ≥ 75 years of age versus patients < 65. These results were similar between doripenem and Comparator treatment groups.
No overall differences in safety were observed between older and younger subjects, but greater sensitivity of some older individuals cannot be ruled cut.
Elderly subjects had greater doripenem exposure relative to non- elderly subjects; however, this increase in exposure was mainly attributed to age-related changes in renal function. This drug is known to be excreted substantially by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function or pre-renal azotemia. Because elderly patients are more likely to have decreased renal function or pre-renal azotemia, care should be taken in dose selection, and it may be useful to monitor renal function.

Patients with Renal Impairment
Dosage adjustment is required in patients with moderately or severely impaired renal function in such patients, renal function should be monitored.

Information for Patients
Patients should be counseled that antibacterial drugs including doripenem should only be used to treat bacterial infections. They do not treat viral infections. When doripenem is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by doripenem or other antibacterial drugs in the future.

PREGNANCY AND LACTATION
Pregnancy Category B
Doripenem was not teratogenic and did not produce effects on ossification, developmental delays or fetal weight following intravenous administration during organogenesis at doses as high as 1 g/kg/day in rats and 50 mg/kg/day in rabbits. There are no adequate and well-controlled studies in pregnant women. Doripenem should only be considered if the benefit to the mother outweighs the risk to the fetus.

Lactation
It is not known whether this drug is excreted in human milk. Caution should be exercised when doripenem is administered to a nursing woman.

USE IN SPECIAL POPULATION
Pediatrics
Safety and effectiveness in pediatric patients have not been established.

Geriatrics
No overall differences in safety were observed between older and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

DRUG INTERACTIONS
Valproic acid: A clinically significant reduction in serum valproic acid concentrations has been reported in patients receiving carbapenem antibiotics and may result in loss of seizure control. Although the mechanism of this interaction is not fully understood, data from *In vitro* and animal studies suggest that carbapenem antibiotics may inhibit valproic acid glucuronide hydrolysis. Serum valproic acid concentrations should be monitored frequently after initiating carbapenern therapy. Alternative antibacterial or anticonvulsant therapy should be considered if serum valproic acid concentrations cannot be maintained in the therapeutic range or a seizure occurs.

Probenecid: Probenecid interferes with the active tubular secretion of doripenem, resulting in increased plasma concentrations of doripenem. Co-administration of probenecid with Doripenem for injection is not recommended.

ADVERSE DRUG REACTIONS
During clinical investigations, adult patients were treated with doripenem (500 mg administered over 1 hour q8h) in the three comparative phase III clinical studies conducted by the innovator; in some patients, parenteral therapy was followed by a switch to an oral antimicrobial. The median age of patients treated with doripenem was 54 years (range 18-90) in the comparative complicated urinary tract infection (cUTI) study and 46 years (range 18-94) in the pooled comparative complicated intra abdominal infection (cIAI) studies. There was a female predominance (62%) in the comparative cUTI study and male prodominance (63%) in the pooled cIAI studies. The patients treated with doripenem were predominantly Caucasian (77%) in the three pooled phase III studies.

The most common adverse reaction (≥ 5%) observed in the doripenem clinical trial were headache, nausea, diarrhea, rash and phlebitis. During clinical trials, adverse drug reactions that led to doripenem discontinuation were nausea (0.2%), vulvomycotic infection (0.1%) and rash (0.1%).
Adverse reactions due to doripenem 500 mg q8h that occurred at a rate ≥ 1% in either indication are listed in table below. Hypersensitivity reactions related to intravenous study drug and *C. difficile* colitis occurred at a rate of less than 1% in the controlled phase III clinical trial.

Table : Adverse Reactions*with incidence Rates (%) of ≥1% and Adverse Events † Having Clinically Important Difference in Frequency by Indication in Three Controlled, Comparative Doripenem Phase III Clinical Trials Conducted by the Innovator.

System organ class	Complicated Urinary Tract Infections (One Trial)		Complicated Intra Abdominal Infections (Two Trials)	
	Doripenem 500 mg administered every 8 hours (n =376)	Levofloxacin 250 mg administered IV every 24 hours (n =372)	Doripenem 500 mg administered every 8 hours (n =477)	Meropenem 1 g administered every 8 hours (n =469)
Nervous system disorders				
Headache	16	15	4	5
Vascular disorders				
Phlebitis	4	4	8	6
Gastro-intestinal disorders				
Nausea	4	6	12	9
Diarrhea	6	10	11	11
Blood and lymphatic system disorders				
Anemia††	2	1	10	5
Renal and urinary disorders				
Renal impairment/Renal failure††	<1	0	1	<1
Skin and subcutaneous disorders				
Pruritus	<1	1	3	2
Rash*	1	1	5	2
Investigations				
Hepatic enzyme elevation**	2	3	1	3
Infection and Infestations				
Oral candidiasis	1	0	1	2
Vulvomycotic infection	2	1	1	<1

*An adverse drug reaction was defined as an undesirable effect, reasonably associated with the use of Doripenem that may occur as part of its pharmacological action or may be unpredictable in its occurrence.

Postmarketing experience: The following treatment-emergent adverse events (known to occur with ß-lactams including carbapenems) have been reported voluntarily during post approval use of doripenem. They are included due to their seriousness, although it is not possible to estimate their frequency and casualty has not been established:

- Anaphylaxis
- Stevens-Johnson Syndrome
- Toxic epidermal necrolysis
- Interstitial pneumonia
- Seizure

OVERDOSE AND TREATMENT
In the event of overdose, doripenem should be discontinued and general supportive treatment should be given. Doripenem can be removed by hemodialysis. In subjects with end-stage renal disease with administered doripenem 500 mg, the mean total recovery of doripenem and doripenem-M1 in the dialysate following a 4-hour hemodialysis session was 259 mg (52% of the dose). However, no information is available on the use hemodialysis to treat overdosage.

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction report to the FDA:www.fda.gov.ph.
Seek medical attention immediately at the first sign of any adverse drug reaction.

STORAGE CONDITION
Store at temperatures not exceeding 30°C.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN.

AVAILABILITY
USP Type I plain tubular glass vial with rubber closure & white flip-off seal (Box of 1's)

DRP-13150
Date of First Authorization: March 11, 2015
Date of Revision of Package Insert: October 12, 2023

Manufactured by:
MEPROMAX LIFESCIENCES PVT. LTD.
Plot No. 16, Pharma City, Selaqui Distt.
Dehradun, Uttarakhand, India

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BDR PHARMACEUTICALS INTERNATIONAL PVT. LTD.
407/408, Sharda Chambers, 29 New Marine Lines,
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AMBICA INTERNATIONAL CORPORATION
No. 9 Amsterdam Extension, Merville Park Subd.,
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FGTDRAXPH/I1

Size : 200 x 320 mm
54 gsm Maplitho paper