Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986
This medicine is dispensed with a doctor's prescription only

INREBIC
100 mg, capsules

Name and quantity of active ingredient:
Each capsule of INREBIC contains 100 mg fedratinib (as dihydrochloride monohydrate).

Inactive ingredients - See section 6 under 'Additional information' and section 2 under 'Important information about some of this medicine's ingredients'.

Read the entire leaflet carefully before you start using this medicine. This leaflet contains concise information about this medicine. If you have any further questions, consult your doctor or pharmacist.

This medicine has been prescribed to treat you. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar to yours.

What is the most important information I should know about INREBIC?
INREBIC may cause serious side effects, including:

- **Encephalopathy (including Wernicke's encephalopathy).** A serious and sometimes fatal neurological problem called encephalopathy (including Wernicke's encephalopathy) has happened in some people who take INREBIC.
  Wernicke's encephalopathy is a neurologic emergency that can happen if you do not have enough vitamin B1 (thiamine) in your body. Your doctor will do a blood test to check your vitamin B1 level before starting and during treatment with INREBIC. Your doctor may tell you to stop taking INREBIC and take a vitamin B1 supplement if you develop side effects during treatment with INREBIC.

Call your doctor right away if you develop diarrhea, nausea, or vomiting that does not respond to treatment.

Get emergency medical help right away if you develop the following:
- ○ confusion, memory problems or drowsiness
- ○ problems with balance and movement, such as difficulty walking
- ○ eye problems, such as double or blurred vision or abnormal eye movements

Call your doctor if you experience rapid weight loss or weight loss that does not get better with treatment.

1. What is this medicine intended for?

INREBIC is indicated for the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF).

Therapeutic group: antineoplastic agents, protein kinase inhibitor

2. Before using this medicine

Do not use this medicine if:
- You are sensitive (allergic) to fedratinib or to any of the other ingredients of this medicine (listed in section 6).

Special warnings about using this medicine
- See **'What is the most important information I should know about INREBIC?'** at the top of this leaflet

Before treatment with INREBIC, tell your doctor if:
- you have low red blood cell or platelet counts (see 'Tests and follow-up')
- you have or have had liver problems (see 'Tests and follow-up')
- you have or have had kidney problems (see 'Tests and follow-up')
- you have had cancer in the past
- you are a current or past smoker
- you have had a blood clot, heart attack, other heart problems, or stroke
- you are breastfeeding or plan to breastfeed (see 'Pregnancy and breastfeeding')
- you have or have had pancreas problems (see 'Tests and follow-up').

Children and adolescents
This medicine is not intended for children and adolescents under 18 years old. There is no information about the safety and efficacy of using this medicine in children and adolescents under 18 years old.

Tests and follow-up
Your doctor will do blood tests before you start, during treatment and as medically necessary to check:
- thiamine level (vitamin B1)
- complete blood count with platelets
- creatinine, blood urea nitrogen (BUN) whose levels show kidney function
- liver function
- amylase and lipase whose levels show pancreas function

Your doctor may adjust the dose or stop treatment based on the results of the blood tests.

Other medicines and INREBIC:
If you are taking, have recently taken, or might take other medicines, including non-prescription medications and dietary supplements, tell your doctor or pharmacist.
INREBIC and other medicines may affect each other causing unwanted side effects. Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

The following medicines may increase the risk of side effects with INREBIC:
- ketoconazole, fluconazole (used to treat fungal infections)
- fluvoxamine (used to treat depression)
- ritonavir (used to treat HIV infections/AIDS)

The following medicines may reduce the effectiveness of INREBIC:
- rifampicin (used to treat tuberculosis (TB) and some other infections)
- phenytoin (used to treat epilepsy and control fits or convulsions)
- efavirenz (used to treat HIV infections/AIDS)

INREBIC may affect other medicines:
- midazolam (used to help you sleep or relieve anxiety)
- omeprazole (used to treat stomach problems)
- metoprolol (used to treat angina or high blood pressure)
- metformin (used to lower blood sugar levels)
- also simvastatin and dextromethorphan

Using this medicine and food
The capsule can be taken either with or without food.
Taking INREBIC with a high fat meal may help to reduce nausea and vomiting symptoms.

Pregnancy and breastfeeding
Pregnancy
There is no information about using INREBIC in pregnant women. If you are pregnant, consult your doctor.

Breastfeeding
It is not known if INREBIC passes into your breast milk. You should not breastfeed during treatment with INREBIC and for at least one month after your last dose. Talk to your doctor about the best way to feed your baby during your treatment with INREBIC.

Driving and using machines
INREBIC has a minor influence on driving and using machines.
If you feel dizzy, do not drive or operate machines until these side effects have gone away.

Important information about some of this medicine's ingredients
Sodium content
This medicine contains less than 1 millimole sodium (23 mg) per dose and is considered 'sodium-free'.

3. How to use this medicine?

- Always use INREBIC according to your doctor's instructions. Check with your doctor or pharmacist if you are not sure about your dose or about how to take INREBIC.
- Do not change your dose or stop taking INREBIC unless your doctor tells you to.

Only your doctor will determine your dose and how you should take this medicine. The usual dose is:
- 400 mg (4 capsules of 100 mg) taken by mouth once daily.
- Your doctor may decide to lower your dose if you are taking certain medicines during your treatment with INREBIC or if you have severe kidney failure.
- If you get certain side effects, your doctor may lower your dose or pause or stop treatment.

Do not exceed the recommended dose.

How to take this medicine
- Swallow the capsules whole, preferably with water.
- Do not open, break or chew the capsules. There is no information about opening capsules and releasing their content.
- The capsules can be taken either with or without food; but it is preferable to take INREBIC with food to avoid nausea.

If you have accidentally taken a higher dose
If you have taken an overdose, or if a child has accidentally swallowed some medicine, immediately see a doctor or go to a hospital emergency room and bring the medicine package and this leaflet with you.

If you forget to take the medicine, skip the missed dose and take your next scheduled dose at your regular time the next day.
Do not take 2 doses to make up for the missed dose.

Adhere to the treatment as recommended by your doctor.
Even if your health improves, do not stop treatment with this medicine without consulting your doctor.

If you stop taking INREBIC
- Do not stop taking INREBIC unless your doctor tells you to.

Do not take medicines in the dark! Check the label and dose every time you take medicine. Wear glasses if you need them.

If you have any further questions about using this medicine, consult your doctor or pharmacist.

4. Side effects

Like with all medicines, using INREBIC may cause side effects in some users. Do not be alarmed by this list of side effects; you may not experience any of them.

INREBIC may cause serious side effects, including:
- See '**What is the most important information I should know about INREBIC?**' at the top of this leaflet.
- **Low blood cell counts.** INREBIC may cause low red blood cell counts (anemia) and low platelet counts (thrombocytopenia) in some people. You may need a blood transfusion if your blood counts drop too low. Your doctor will do blood tests to check your blood counts before you start and during treatment with INREBIC. Tell your doctor if you develop any bleeding or bruising during treatment with INREBIC.
- **Nausea, vomiting, and diarrhea.** Your doctor may give you certain medicines to help treat your nausea, vomiting, and diarrhea.
  Call your doctor or get emergency medical help right away if you have nausea, vomiting, or diarrhea that does not get better with treatment.
- **Liver problems.** Your doctor will do blood tests to check your liver function before starting and during treatment with INREBIC.
- **Amylase and lipase increases.** You may have changes in your blood amylase or lipase levels that may indicate a problem with your pancreas. Your doctor will do blood tests to check your blood amylase or lipase levels before starting and during treatment with INREBIC.
- **Increased risk of major cardiac events such as heart attack, stroke, or death in people who have cardiovascular risk factors and who are current or past smokers while using another JAK inhibitor to treat rheumatoid arthritis.**
  Get emergency help right away if you have any symptoms of a heart attack or stroke while taking INREBIC, including:
  - ○ discomfort in the center of your chest that lasts for more than a few minutes, or that goes away and comes back
  - ○ severe tightness, pain, pressure, or heaviness in your chest, throat, neck, or jaw
  - ○ pain or discomfort in your arms, back, neck, jaw, or stomach
  - ○ shortness of breath with or without chest discomfort
  - ○ breaking out in a cold sweat
  - ○ nausea or vomiting
  - ○ feeling lightheaded
  - ○ weakness in one part or on one side of your body
  - ○ slurred speech
- **Increased risk of blood clots.** Blood clots in the veins of your legs (deep vein thrombosis, DVT) or lungs (pulmonary embolism, PE) have happened in people taking another JAK inhibitor for rheumatoid arthritis and may be life-threatening.
  Tell your doctor right away if you have any signs and symptoms of blood clots during treatment with INREBIC, including:
  - ○ swelling, pain, or tenderness in one or both legs
  - ○ sudden unexplained chest or upper back pain
  - ○ shortness of breath or difficulty breathing
- **Possible increased risk of new (secondary) cancers.** People who take another JAK inhibitor for rheumatoid arthritis have an increased risk of new (secondary) cancers, including lymphoma and other cancers. People who smoke or who smoked in the past have an added risk of new cancers.

Additional side effects:
Very common side effects - affect more than one in ten users:
- diarrhea
- nausea
- low red blood cell counts (anemia)
- vomiting
- tiredness or weakness
- low platelet counts (thrombocytopenia)
- constipation
- muscle spasms
- blood creatinine increased
- pain in extremities
- low white blood cell counts (neutropenia)
- increased liver enzyme levels in blood (ALT and AST)
- increased pancreas enzymes level (lipase and amylase)
- low level of sodium in the blood (hyponatremia)

Common side effects - affect 1-10 in 100 users:
- heart failure
- cardiogenic shock
- reduced blood supply to the heart muscle (myocardial ischemia)
- headache
- weight increased
- dizziness
- bone pain
- urinary tract infection
- painful urination
- high blood pressure

These are not all of the possible side effects of INREBIC.
Call your doctor for medical advice about side effects.

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your doctor.

You can report side effects to the Ministry of Health by following the link 'Reporting Side Effects of Drug Treatment' on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects. You can also use this link: https://sideeffects.health.gov.il

5. How to store the medicine?

- Prevent poisoning! To prevent poisoning, keep this and all other medicines in a closed place, out of the reach and sight of children and/or infants. Do not induce vomiting unless explicitly instructed to do so by your doctor.
- Do not use the medicine after the expiry date (exp. date) which is stated on the package/bottle label. The expiry date refers to the last day of that month.

Storage conditions
- This medicine does not require any special temperature storage conditions. It is recommended to keep in room temperature. Keep the bottle tightly closed in order to protect from moisture.

6. Additional information

- In addition to the active ingredient, this medicine also contains:
  - *Capsule content:*
    silicified microcrystalline cellulose (SMCC) and sodium stearyl fumarate.
  - *Capsule shell:*
    gelatin, red iron oxide, titanium dioxide.
  - *Printing ink:*
    shellac glaze in ethanol, titanium dioxide, isopropyl alcohol, N-butyl alcohol, propylene glycol.

What the medicine looks like and contents of the pack
- INREBIC are reddish-brown capsules, printed with "FEDR" on the cap and "100 mg" on the body in white ink.

Pack sizes:
- bottle containing 120 capsules

Registration holder's name and address
Bristol-Myers Squibb (Israel) Ltd.,
18 Aharon Bart St. P.O Box 3361,
Kiryat Arye,
Petach Tikva

Manufacturer's name and address
Bristol-Myers Squibb Company
430 East 29th Street, 14th Floor New York, New York 10016 USA

Revised in December 2021 according to the MOH guidelines.

Registration number of the medicine in the Ministry of Health's National Drug Registry:
INREBIC: 168-28-36598-99