PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS REGULATIONS (PREPARATIONS) 1986

This medicine is marketed upon physician prescription only

TEMODAL®

5 mg, 20 mg, 100 mg, 250 mg
Capsules

Each capsule contains:
Temozolomide 5 mg, 20 mg, 100 mg, 250 mg

For a list of inactive ingredients see section 6 "**Further Information**". See also section 2.7 "**Important information about some of the ingredients of TEMODAL**".

Read all of this leaflet carefully before you start taking this medicine.

- This leaflet contains concise information about the medicine. If you have any further questions, refer to the doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their medical condition seems similar to yours.
- This medicine is not intended for children under 3 years of age, since there are no data related to the use in patients under the age of 3 years. The data about children above the age of 3 years are limited.

1. WHAT TEMODAL IS INTENDED FOR?

1.1 What is TEMODAL?

TEMODAL contains a medicine called temozolomide. This medicine is an antitumour agent for the treatment of specific forms of brain tumours.
TEMODAL belongs to a group of medicines called cytotoxic or chemotherapy medicines.
Therapeutic group: Antineoplastic preparation.

1.2 What is TEMODAL used for?

TEMODAL capsules are indicated for the treatment of:

- Adult patients suffering from newly diagnosed glioblastoma multiforme (a specific form of brain tumour) in a combination treatment with radiation and subsequently as monotherapy treatment;
- Children above the age of 3 years, adolescents and adults suffering from malignant glioma such as glioblastoma multiforme or anaplastic astrocytoma (specific forms of brain tumours), showing recurrence or progression after standard therapy;
- **TEMODAL** capsules are also indicated as first line treatment for adult patients with advanced metastatic malignant melanoma.

2. BEFORE USING TEMODAL

2.1 Do not use TEMODAL if:

- you are sensitive (allergic) to temozolomide or any of the other ingredients of this medicine (listed in section 6).
- you have had an allergic reaction to dacarbazine (an anticancer medicine sometimes called DTIC). Signs of allergic reaction include feeling itchy, breathlessness or wheezing, swelling of the face, lips, tongue or throat.
- certain kinds of blood cells are severely reduced (myelosuppression), such as your white blood cell count and platelet count. These blood cells are important for fighting infection and for proper blood clotting. Your doctor will check your blood to make sure you have enough of these cells before you begin treatment.
- you are pregnant or breast-feeding.

2.2 Special Warnings and precautions concerning use of TEMODAL
Talk to your doctor, pharmacist or nurse before taking **TEMODAL**,
- as you should be observed closely for the development of a serious form of chest infection called *Pneumocystis jirovecii* pneumonia (PCP). If you are a newly-diagnosed patient (glioblastoma multiforme) you may be receiving **TEMODAL** for 42 days in combination with radiotherapy. In this case, your doctor will also prescribe medicine to help you prevent this type of pneumonia (PCP).
- if you have ever had or might now have a hepatitis B infection. This is because **TEMODAL** could cause hepatitis B to become active again, which can be fatal in some cases. Patients will be carefully checked by their doctor for signs of this infection before treatment is started.
- if you have low counts of red blood cells (anaemia), white blood cells and platelets, or blood clotting problems before starting the treatment, or if you develop them during treatment. Your doctor may decide to reduce the dose, interrupt, stop or change your treatment. You may also need other treatments. In some cases, it may be necessary to stop treatment with **TEMODAL**. Your blood will be tested frequently during treatment to monitor the side effects of **TEMODAL** on your blood cells.
- as you may have a small risk of other changes in blood cells, including leukaemia.
- if you have nausea (feeling sick in your stomach) and/or vomiting which are very common side effects of **TEMODAL** (see section 4), your doctor may prescribe you a medicine (an anti-emetic) to help prevent vomiting.
  If you vomit frequently before or during treatment, ask your doctor about the best time to take **TEMODAL** until the vomiting is under control. If you vomit after taking your dose, do not take a second dose on the same day.
- if you develop fever or symptoms of an infection, contact your doctor immediately.
- if you are older than 70 years of age, you might be more prone to infections, bruising or bleeding.
- if you have liver or kidney problems, your dose of **TEMODAL** may need to be adjusted.
- When using the medicine, there is a risk of liver damage, including liver failure that may be life-threatening. Therefore, it is necessary to perform liver function tests before and during treatment with **TEMODAL.**

2.3 Interactions with other medicines
If you are taking or have recently taken other medicines, including non-prescription medicines and nutritional supplements, you should tell the attending doctor or pharmacist. Especially inform your doctor or pharmacist if you are taking: other medicines used to treat cancer, other myelosuppressants, or valproic acid.

2.4 Taking TEMODAL with food and drink
Take the capsules on an empty stomach; for example, at least one hour before you plan to eat breakfast. Swallow the capsule(s) whole with a glass of water.

2.5 Pregnancy, breast-feeding and fertility
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. This is because you must not be treated with **TEMODAL** during pregnancy unless clearly indicated by your doctor.

Effective contraceptive precautions must be taken by female patients who are able to become pregnant during treatment with **TEMODAL** and for at least 6 months following completion of treatment.

You should stop breast-feeding while receiving treatment with **TEMODAL**.

Male fertility
TEMODAL may cause permanent infertility. Male patients should use effective contraception and not father a child for at least 3 months after stopping treatment. It is recommended to seek advice on conservation of sperm prior to treatment.

2.6 Driving and using machines
TEMODAL may make you feel tired or sleepy. In this case, do not drive or use any tools or machines or cycle until you see how this medicine affects you (see section 4).

2.7 Important information about some of the ingredients of TEMODAL
TEMODAL contains lactose
This medicine contains lactose (a kind of sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

TEMODAL contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

2.8 Children and adolescents
Do not give this medicine to children under the age of 3 years because it has not been studied. **TEMODAL** is intended for the treatment of children from the age of 3 years for different forms of brain tumours (such as glioblastoma multiforme or anaplastic astrocytoma), showing recurrence or progression after standard therapy. Nevertheless, information in children over the age of 3 years is limited.

3. HOW SHOULD YOU USE TEMODAL?
Always take **TEMODAL** exactly as your doctor has told you. It is very important to check with your doctor or pharmacist if you are not sure. Errors in how you take this medicine may have serious health consequences.
Do not exceed the recommended dose.

This medicine is not intended for administration to infants and children under 3 years of age.
Your doctor will decide the exact **TEMODAL** dose you should take, based on your body size (height, weight) and whether or not you have had chemotherapy treatment in the past. You may be asked to take another medicine before or after taking **TEMODAL** to prevent or control nausea and vomiting.

How to take the medicine (for all patients):
Take the prescribed **TEMODAL** dose once a day on an empty stomach, for example, at least one hour before breakfast. It is preferable to take the dose at the same time every day. Swallow the capsule whole with a glass of water.
Do not open, crush or chew the capsule. **TEMODAL** belongs to a group of medicines called cytotoxic or chemotherapy medicines. If capsules are opened, this creates a risk for unintended exposure to the drug through inhalation or contact with the skin or mucous membranes. To reduce the risk of unintended exposure to **TEMODAL**, capsules should not be opened. If the capsule is damaged, avoid contact of the powder of the capsule with the skin and mucous membranes (eyes, nose) (see section 2). In case of powder contact, the hands should be washed.

Depending on the dosage that will be prescribed for you, you may need to swallow more than one capsule at a time and you may need to swallow capsules of different doses together (dose - the amount of active ingredient in the capsule, in milligrams). The color of the capsule cap and the writing on the capsules is different for each strength (see details in table below).

Strength	Colour of the cap
TEMODAL 5 mg capsules	green
TEMODAL 20 mg capsules	yellow
TEMODAL 100 mg capsules	pink
TEMODAL 250 mg capsules	white

You should make sure you fully understand and remember the following:
- how many capsules you need to take every dosing day. Ask your doctor or pharmacist to write it down (including the colour).
- which days are your dosing days - the days you need to take your medicine.

Review the dose with your doctor each time you start a new cycle, since it may be different from the last cycle.

Tests and follow-up
During the course of treatment, you must undergo blood tests frequently to monitor the status of your blood cells.
In addition, a liver function test will be performed before and during the course of treatment, since there is a risk of liver damage that may even be life-threatening (also see section 2).

In case of vomiting after taking the medicine, do not take another dose that same day.

If you have accidentally taken a higher dose than you should
If you accidentally take more **TEMODAL** capsules than you were told to, contact your doctor, pharmacist or nurse immediately.

If you forget to take TEMODAL
Take the missed dose as soon as possible during the same day. If a full day has gone by, check with your doctor. Do not take a double dose to make up for a forgotten dose, unless your doctor tells you to do so.

Do not take medicines in the dark! Check the label and the dose <u>each time</u> you take your medicine. Wear glasses if you need them.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. SIDE EFFECTS
As with other medicines, **TEMODAL** may cause side effects, in some users. Do not be alarmed by reading the list of side effects, you may not suffer from any of them.

<u>Contact your doctor **immediately** if you have any of the following:</u>
- a severe allergic (hypersensitive) reaction (hives, wheezing or other breathing difficulty),
- uncontrolled bleeding,
- seizures (convulsions),
- fever,
- chills,
- severe headache that does not go away.

TEMODAL treatment can cause a reduction in certain kinds of blood cells. This may cause you to have increased bruising or bleeding, anaemia (a shortage of red blood cells), fever, and reduced resistance to infections. The reduction in blood cell counts is usually short-lived. In some cases, it may be prolonged and may lead to a very severe form of anaemia (aplastic anaemia). Your doctor will monitor your blood regularly for any changes, and will decide if

any specific treatment is needed. In some cases, your **TEMODAL** dose will be reduced or treatment stopped.

Other side effects that have been reported are listed below:

Very Common side effects (may affect more than 1 in 10 people) are:
- loss of appetite, difficulty speaking, headache
- vomiting, nausea, diarrhoea, constipation
- rash, hair loss
- tiredness

Common side effects (may affect up to 1 in 10 people) are:
- infections, oral infections
- reduced number of blood cells (neutropenia, lymphopenia, thrombocytopenia)
- allergic reaction
- increased blood sugar
- memory impairment, depression, anxiety, confusion, inability to fall asleep or stay asleep
- impaired coordination and balance
- difficulty concentrating, change in mental status or alertness, forgetfulness
- dizziness, impaired sensations, tingling sensations, shaking, abnormal taste
- partial loss of vision, abnormal vision, double vision, painful eyes
- deafness, ringing in the ears, earache
- blood clot in lung or legs, high blood pressure
- pneumonia, shortness of breath, bronchitis, cough, inflammation of your sinuses
- stomach or abdominal pain, upset stomach/heartburn, difficulty swallowing
- dry skin, itching
- muscle damage, muscle weakness, muscle aches and pain
- painful joint, back pain
- frequent urination, difficulty withholding your urine
- fever, flu-like symptoms, pain, feeling unwell, a cold or the flu
- fluid retention, swollen legs
- liver enzyme elevations
- loss of weight, weight gain
- radiation injury

Uncommon side effects (may affect up to 1 in 100 people) are:
- brain infections (meningoencephalitis herpetic) including fatal cases
- wound infections
- new or reactivated cytomegalovirus infections
- reactivated hepatitis B virus infections
- secondary cancers including leukaemia
- reduced blood cell counts (pancytopenia, anaemia, leukopenia)
- red spots under the skin
- diabetes insipidus (symptoms include increased urination and feeling thirsty), low potassium level in the blood
- mood swings, hallucination
- partial paralysis, change in your sense of smell
- hearing impairment, infection of the middle ear
- palpitations (when you can feel your heart beat), hot flushes

- swollen stomach, difficulty controlling your bowel movements, haemorrhoids, dry mouth
- hepatitis and injury to the liver (including fatal liver failure), cholestasis, increased bilirubin
- blisters on body or in mouth, skin peeling, skin eruption, painful reddening of the skin, severe rash with skin swelling (including palms and soles)
- increased sensitivity to sunlight, urticaria (hives), increased sweating, change in skin colour
- difficulty in urinating
- vaginal bleeding, vaginal irritation, absent or heavy menstrual periods, breast pain, sexual impotence
- shivering, face swelling, discolouration of the tongue, thirst, tooth disorder
- dry eyes

If a side effect appears, if any of the side effects gets serious or if you suffer from a side effect not mentioned in this leaflet, consult your doctor.

Side effects can be reported to the Ministry of Health by using the link "Adverse Drug Reactions Report" at the home page of the Ministry of Health's web site (www.health.gov.il) which refers to the online side effects reporting form, or by using the link: https://sideeffects.health.gov.il/

5. HOW TO STORE TEMODAL?

- Avoid Poisoning! This medicine and any other medicine must be stored in a safe place out of the sight and reach of children and/or infants, preferably in a locked cupboard, in order to avoid poisoning. Accidental ingestion can be lethal for children. Do not induce vomiting unless explicitly instructed to do so by a doctor.
- Do not use this medicine after the expiry date (exp. date) which is stated on the label and carton. The expiry date refers to the last day of that month.

- **Storage Conditions**: Do not store above 25°C.

  Tell your pharmacist if you notice any change in the appearance of the capsules.

- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. FURTHER INFORMATION

In addition to the active ingredient **TEMODAL** also contains:
Capsule content:
Anhydrous lactose, sodium starch glycolate, stearic acid, tartaric acid, colloidal anhydrous silica (see section 2.7 "**Important information about some of the ingredients of TEMODAL**").

TEMODAL 5 mg capsules: Each capsule contains 132.8 mg of anhydrous lactose.
TEMODAL 20 mg capsules: Each capsule contains 182.2 mg of anhydrous lactose.
TEMODAL 100 mg capsules: Each capsule contains 175.7 mg of anhydrous lactose.
TEMODAL 250 mg capsules: Each capsule contains 154.3 mg of anhydrous lactose.

Capsule shell:
TEMODAL 5 mg capsules: gelatin, titanium dioxide, sodium lauryl sulfate, yellow iron oxide, FD & C Blue 2.
TEMODAL 20 mg capsules: gelatin, titanium dioxide, yellow iron oxide, sodium lauryl sulfate.
TEMODAL 100 mg capsules: gelatin, titanium dioxide, sodium lauryl sulfate, red iron oxide.

TEMODAL 250 mg capsules: gelatin, titanium dioxide, sodium lauryl sulfate.

Printing ink:
Shellac, anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, purified water, ammonium hydroxide, potassium hydroxide, and black iron oxide.

What **TEMODAL** looks like and contents of the pack
TEMODAL 5 mg capsules have an opaque white body, an opaque green cap, and are imprinted with black ink. The cap is imprinted with “TEMODAL”. The body is imprinted with "5 mg", the Schering-Plough logo and two stripes.
TEMODAL 20 mg capsules have an opaque white body, an opaque yellow cap, and are imprinted with black ink. The cap is imprinted with “TEMODAL”. The body is imprinted with "20 mg", the Schering-Plough logo and two stripes.
TEMODAL 100 mg capsules have an opaque white body, an opaque pink cap, and are imprinted with black ink. The cap is imprinted with “TEMODAL”. The body is imprinted with "100 mg", the Schering-Plough logo and two stripes.
TEMODAL 250 mg capsules have an opaque white body and cap and are imprinted with black ink. The cap is imprinted with “TEMODAL”. The body is imprinted with "250 mg", the Schering-Plough logo and two stripes.

Pack sizes: Sachet presentation
The capsules for oral use are individually sealed in sachets and dispensed in cartons containing 5 or 20 capsules.

Not all pack sizes may be marketed.

License Holder and Importer:
Merck Sharp & Dohme (Israel - 1996) Company Ltd., 34 Ha'charash St., Hod-Hasharon.

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Drug registration no. listed in the official registry of the Ministry of Health:
TEMODAL 5 mg: 120.28.30114
TEMODAL 20 mg: 120.29.30115
TEMODAL 100 mg: 120.30.30116
TEMODAL 250 mg: 120.31.30119