Palestinian Ministry of Health
General Administration of pharmacy

Treatment Guidelines
for Use of
Restricted Drugs & Biologics

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المقدمة

حرصاً على الإرتقاء بجودة الخدمات الصحية في وزارة الصحة للأفضل, يجب تطبيق سياسة دوائية فعالة تعمل على ترشيد الاستهلاك للأدوية. وذلك يتطلب إجراء مراجعات دائمة للإجراءات العلاجية , ووضع آليات وقوانين تحدد استخدام الأدوية .

والسياسة الدوائية , هي جزء أساسي من السياسة الصحية. وأهدافها الأساسية ترتكز على: الاستمرارية في التوفير العادل للأدوية, و القدرة على تحمل التكاليف الخاصة بها. ويتحقق ذلك ,بالاعتماد على الاستخدام السليم للأدوية من قبل المهنيين الصحيين, والمستهلكين من حيث التكلفة و الفعالية العلاجية.

ولأن الوضع الدوائي يؤثر على مستوى الخدمات الصحية المقدمة, وحيث أن الخدمات الصحية تفقد مصداقيتها إذا لم يكن هناك إمدادات كافية من الأدوية (علما أن نفقات الأدوية هي من أهم مكونات النفقات الصحية على المستوى الاقتصادي) مما يبرز أهمية الشؤون المالية في ميدان الدواء; لذلك تعمل الإدارة العامة للصيدلة على حث الاستخدام الرشيد للأدوية, وتفعيل دور الصيدلاني السريري في المراكز الصحية.

وضمن خططها, عملت على إحداث لجان مكلفة: بمراجعة مشاكل الإسراف وسوء وصف الدواء، ومراجعة استعمال الأدوية الجديدة مرتفعة السعر; لوضع دليل يضم أفضل البيانات العلمية المؤكدة للفعالية إلى جانب رأي الخبراء; حرصاً منها على ترشيد استخدام الدواء, الذي يحمي صحة المواطن من الآثار الصحية الضارة للاستعمال غير الرشيد للدواء.

مدير عام الإدارة العامة للصيدلة
الدكتورة رانيا شاهين

Restricted Drugs

Adalimumab 40mg prefilled syringe

Indication:

1. Active crohn's disease (moderate to severe), in patients with inadequate response or intolerant to conventional therapy.
2. Ulcerative colitis in patients with moderate-to-severe active disease , who have an inadequate response to immunosuppressants or intolerant to conventional therapy. All patients must have a Mayo score of 6 to 12 and an endoscopy sub score of 2 to 3.
3. Active rheumatoid arthritis (moderate to severe). IF the treatment with traditional DMARDS and Etanercept failed.

Level of prescriber

Adalimumab should be prescribed by GIT specialist, Internist or rheumatologist. The prescriber should write a report about the patient condition that necessitates its use. The report should contain in details all the previous treatment stages and it should be updated every six months for indications that need more than six months of treatment.

Dose and dose adjustment.

Crohn's Disease: For SQ use only . 160 mg initially on Day 1 (given as 4 injections on day 1 or as 2 injections on day 1 and 2), followed by 80 mg two weeks later (Day 15). Start maintenance dosage of 40 mg once every other week on day 29.

Ulcerative colitis: initial dose of 160 mg, a second dose 2 weeks later of 80 mg, and a maintenance dose of 40 mg every other week, thereafter. The drug should only continue to be used in patients who have shown evidence of clinical remission by 8 weeks of therapy.

Rheumatoid arthritis: child ≥ 30kg wt. and adult dose : 40 mg administered every other week.

- Safety and efficacy not established in children younger than 4 years; there are limited data in treating children who weigh less than 15 kg.

Cautions

- Serious infection risk (Active TB , nvasive fungal infections, bacterial Legionella, Listeria), and viral (hepatitis B , CMV)
- Discontinue if patient develops serious infection or sepsis until treated.
- Worsening or new-onset congestive heart failure reported with TNF blockers
- Consider DC if hematologic disorder occurs (thrombocytopenia, pancytopenia, leukopenia)
- Increased risk of lymphoma and other cancers reported in children and adolescents
- Occurrence of leukemia and new-onset psoriasis reported in patients treated with TNF blockers
- Potential increased risk of malignancy when coadministered with azathioprine or 6-mercaptopurine or for elderly group

Duration of treatment:
For (52) weeks. (One year) in Crohn's, 1-2 years for RA.

Unit price (MOH tenders):
Adalimumab 40mg syringe: 2878 ILS

Storage and Stability:

- Must be refrigerated at 2° to 8° C. Once removed from the refrigerator for room temperature storage, the syringe or pen must be used within 14 days or discarded
- **DO NOT FREEZE.**
- **Protect from light.**
- **Follow up and monitoring**
- Place & read PPD before initiation and periodically during therapy. If positive treat for TB then start therapy.
- Monitor improvement of symptoms and physical function assessments,
- CBC, ESR, CRP. Signs of infection, Bleeding, or bruising.

Alprostadil 0.5 mg\ml

Indication:
For palliative, temporarily maintenance the patency of the ductus arteriosus until Corrective or palliative surgery can be performed in neonates who have congenital heart defects and who depend upon a patent ductus arteriosus for survival.
Level of prescriber : pediatric -neonatal specialist.

Contraindication:
Alprostadil is contraindicated in the following patients:
1. Cyanotic neonates with persistent fetal circulation.(should not be used in neonates with respiratory distress syndrome).
2. Neonates with total anomalous pulmonary venous return below the diaphragm, neonates with polysplenia or asplenia in whom pulmonary atresia is combined with anomalous pulmonary venous return which may be obstructed.

In such patients Alprostadil may precipitate pulmonary edema because of increased pulmonary blood flow.

Dosage:
The recommended starting dose of PGE_1 is 0.05-0.1 mcg/kg/min., higher doses do not offer added benefit.
When the desired effect on the ductus arteriosus is achieved, decrease infusion to the lowest possible dose while maintaining the desired effect. This may be accomplished by reducing the dosage from 0.1 to 0.05 to 0.025 to 0.01 mcg\Kg of body weight per minute.
Preferably administer via large vein; alternatively, administer through umbilical artery catheter

Dose Adjustment:
- The dose may be titrated to maintain an open ductus with the use of clinical signs of adequate perfusion, in addition to arterial blood pH and

PO_2, arterial blood pressure, pulse, urine output, and echocardiography.
- Doses up to 0.4 mcg/kg/min have been required in some patients.
- In most infants, ductus will reopen within 30 mins to 2 hours after starting Alprostadil . With reopening of ductus, PO_2 values typically rise 20-30 mm Hg.
- Once ductus has opened, dose can usually be reduced to 0.002-0.05 mcg/kg/min.

Duration of Treatment:
(alprostadil) appears most effective within 96 hours after birth due to a decreasing responsiveness of the ductus arteriosus with time after birth,.

In most patients, therapy with PGE_1 is continued until balloon atrial septostomy or cardiac surgery is performed.

Unit price (MOH tenders): Alprostadil 0.5 mg\ml: 345 ILS

Necessary Monitoring:
1. Arterial pressure should be monitored by umbilical artery catheter, auscultation, or with a Doppler transducer.
2. In infants with restricted pulmonary blood flow, measure efficacy of Alprostadil injection by monitoring improvement in blood oxygenation.
3. In infants with restricted systemic blood flow, measure efficacy by monitoring improvement of systemic blood pressure and blood pH.
4. Respiratory status should be monitored throughout treatment, and Alprostadil Injection, should be used where ventilatory assistance is immediately available (because apnea is experienced by about 10 to 12% of neonates with congenital heart defects treated with Alprostadil Injection, apnea is most often seen in neonates weighing < 2 kg at birth and usually appears during the first hour of drug infusion.
5. Because Alprostadil inhibits platelet aggregation, used cautiously in neonates with bleeding tendencies.

Stability and Storage Recommendations: Store Alprostadil in a refrigerator at 2° C to 8° C. Prepare fresh dilutions every 24hours. Discard any dilution more than 24 hours old.

Bevacizumab 400 mg vial & 100 mg vial

Indications:

1. Treatment of metastatic colorectal cancer 1st & 2nd line In combination with IV 5–fluorouracil .
2. Treatment of unresectable, locally advanced, recurrent or metastatic nonsquamous nonsmall cell lung cancer in combination with carboplatin and paclitaxel as first-line treatment
3. Treatment of metastatic renal cell carcinoma in combination with interferon alfa.
4. As single-agent therapy for glioblastoma that has progressed despite previous therapy.

Limitation of Use: Bevacizumab is not indicated for adjuvant treatment of colon cancer

Level of Prescriber: Oncologist .The prescriber should write a report about the patient condition that necessitates Bevacizumab use. The report should be updated every six months.

Dose &dose adjustment: IV infusion

Metastatic colorectal cancer

1. First-line treatment: 5-10 mg/kg q 2wks (with fluorouracil based chemotherapy) :
   a. 5 mg/kg when used in combination with bolus-IFL (ie, irinotecan, 5-FU, leucovorin)
   b. 10 mg/kg when used in combination with FOLFOX4(ie, oxaliplatin, 5-FU, leucovorin)
2. 2nd line treatment in patient who have progressed on 1st line bevacizumab containing regimen as 5mg /kg iv q 2wks or 7.5 mg /kg q 3 wks with fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin

Non-Squamous Non-Small Cell Lung Cancer

15 mg/kg every 3 weeks in combination with carboplatin and paclitaxel for up to 6 cycles of treatment followed by AVASTIN as a single agent until disease progression.

Advanced and/or Metastatic Renal Cell Carcinoma
10 mg/kg every 2 weeks in combination with interferon alfa. AVASTIN should be given in combination with IFN alfa-2a (ROFERON A). The recommended IFN alfa-2a dose is 9 MIU three times a week, however, if 9 MIU is not tolerated, dosage may be reduced to 6 MIU and further to 3 MIU three times a week

Relapsed high grade malignant Glioma:
Adults IV infusion 10 mg/kg every 14 days.

Dose adjustment:
Safety & efficacy have not been studied in patients with renal or hepatic impairment or in children and adolescents.

Duration and number of cycles:
It is recommended that AVASTIN treatment be continued until progression of the underlying disease
Metastatic colorectal cancer: (depends on protocol)
In FOLFIRI & Bevacizumab: every 2 weeks until disease progression.
In FOLFOX & Bevacizumab: every 2 weeks until disease progression.
In XELOX & Bevacizumab: every 3 weeks until disease progression.
Non-Squamous Non-Small Cell Lung Cancer: Up to 6 cycles.
Metastatic Renal Cell Carcinoma:
For 6-8 cycles, depending on disease stage.

Unit price (MOH tenders):
Bevacizumab 400 mg vial : 9487 ILS
Bevacizumab 100 mg vial : 2505 ILS

Warning in administration: Dilute in a total volume of 100 mL of 0.9% Sodium Chloride Injection. Do not administer as an intravenous push or bolus.

Never dilute or mix with glucose solution

Stability: Before dilution: stable at 2-8°C. Vials should be protected from light. Do not freeze or shake.

After dilution: Diluted solutions may be stored at 2-8°C for up to 8 hours . In the original carton until time of use.

Efficacy:
1) CT scan q 4-6 cycles or other imagining study.
2) Clinical response
3) CEA tumor marker.

Warning & precautions:
A) Discontinue bevacizumab for:
- Gastrointestinal perforations (gastrointestinal perforations, fistula formation in the gastrointestinal tract, intra-abdominal abscess.
- Wound dehiscence and wound healing complications requiring medical intervention
- Serious hemorrhage (i.e., requiring medical intervention)
- Severe arterial thromboembolic events.
- Hypertensive crisis or hypertensive encephalopathy.
- Reversible posterior leukoencephalopathy syndrome (RPLS)
- Nephrotic syndrome

B) Temporarily suspend bevacizumab:
- At least 4weeks (6 week is preferred) prior to elective surgery & 4 weeks (6 week is preferred) after surgery & only following complete healing
- Severe hypertension not controlled with medical management.
- Moderate to severe proteinuria pending further evaluation.
- Severe infusion reactions

C) Contraindicated:
- In patients with CNS metastasis & thrombocytopenia.
- In patients with recent homoptysis (≥2.5 ml blood).

Capecitabine 500 mg tablets

Indications

1. Treatment of metastatic colorectal cancer. First-line when fluoropyrimidine treatment alone is preferred
2. Treatment of metastatic breast cancer alone or in combination with docetaxel
3. Treatment of metastatic gastric cancer.

Level of prescriber: Oncologist. The prescriber should write a report about the patient condition that necessitates its prescription. The report should be updated every 6 months.

Dose and dose adjustment

- 825-1250 mg/m^2 administered orally twice daily (morning and evening; equivalent to 1650_2500 mg/m^2 total daily dose) for 2 weeks followed by a 1-week rest period given as 3-week cycles.
- Once the dose has been reduced, it should not be increased at a later time. Doses of capecitabine omitted for toxicity are not replaced or restored; instead the patient should resume the planned treatment cycles
- The dose of phenytoin and the dose of coumarin-derivative anticoagulants may need to be reduced when either drug is administered concomitantly with capecitabine.

Dose adjustment in renal impairment

- Mild renal impairment (CL cr 51-80 ml/min): no adjustment of the initial dose
- Moderate renal impairment (CL cr 30-50 ml/min): give 75% of the dose
- Severe renal impairment (CL cr < 30ml/min): use is contraindicated

Dose adjustment in hepatic impairment

- Mild to moderate impairment: no adjustment is needed
- Severe hepatic impairment: no sufficient data

Duration of treatment and number of cycles:

- Metastatic breast: until disease progression.
- Metastatic colorectal cancer: until disease progression.
- Adjuvant metastatic colorectal cancer: 8 cycles.

Unit price (MOH tenders):

Capecitabine 500 mg tablets: (TH) 21620 ILS

Administration and stability:

Administered in 2 divided doses taken 12 hours apart. Doses should be taken with water within 30 minutes after a meal
Capecitabine tablets should not be cut or crushed

Contraindications

- Hypersensitivity to capecitabine or fluorouracil (5-FU)
- Dihydropyrimidine dehydrogenase deficiency
- Severe renal impairment (CrCl <30 mL/min)

Cautions

- Increased toxicity seen when using 1000 mg/sq.meter dose
- Hepatic/renal impairment, CAD, elderly, bone marrow depression.
- Risk of severe diarrhea, particularly in elderly; apply appropriate re-hydration if occurs

Follow up and monitoring.

1. Clinical monitoring for efficacy and toxicity
2. Renal function at baseline & periodically .
3. CBC with differential
4. Hepatic function-

Docetaxel vial 20 mg & 80 mg

Indications:

1. Locally advanced or metastatic breast cancer after failure of prior chemotherapy, adjuvant treatment for patients with operable node-positive breast cancer.
2. Treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy
3. Androgen independent (hormone refractory) metastatic prostate cancer in combination with prednisone.

Level of prescriber :

Docetaxel should be prescribed by oncologist. Who should write a report about the patient condition that necessitates its prescription. The report should be updated (every six months) or if any change in the dose is recommended .

Dose and dose adjustment :

Breast Cancer :

- For locally advanced or metastatic breast cancer after failure of prior chemotherapy, the recommended dose is 60 mg/m^2 to 100 mg/m^2 administered intravenously over 1 hour every 3 weeks.
- For the adjuvant treatment of operable node-positive breast cancer, the recommended dose is 75 mg/m^2 every 3 weeks(for 6 courses),in combination with doxorubicin and cyclophosphamide. Prophylactic G-CSF may be used to mitigate the risk of hematological toxicities

Non-Small Cell Lung Cancer

The recommended dose is 75 mg/m^2 administered IV over 1 hour every 3 weeks. A dose of 100 mg/m2 in patients previously treated with chemotherapy was associated with increased hematologic toxicity, infection, and treatment-related mortality.

Prostate Cancer: The recommended dose is 75 mg/m^2 every 3 weeks as a 1 hour intravenous infusion.

Dose adjustment: Dose adjustment for toxicity

Breast Cancer
Patients who are dosed initially at 100 mg/m^2 and who experience either febrile neutropenia, neutrophils < 500 cells/mm^3 for more than 1 week, or severe or cumulative cutaneous reactions should have dosage adjusted from 100 mg/m^2 to 75 mg/m^2.

If patient continues to experience these reactions, dosage should either be decreased from 75 mg/m^2 to 55 mg/m^2 or treatment should be discontinued.
In adjuvant treatment of breast cancer; Patients who experience febrile neutropenia, grade 3 or 4 stomatitis, severe or cumulative cutaneous reactions or moderate neurosensory signs and/or symptoms should have their dosage reduced from 75 to 60 mg/m^2. If patient continues to experience these reactions at 60 mg/m^2, treatment should be discontinued.

Non-Small Cell Lung Cancer
Monotherapy:
Patients who are dosed initially at 75 mg/m^2 and who experience either febrile neutropenia, neutrophils< 500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions, or other grade 3/4 non-hematological toxicities during treatment should have treatment withheld until resolution of the toxicity and then resumed at 55 mg/m^2. Patients who develop ≥ grade 3 peripheral neuropathy should have treatment discontinued entirely.

Combination therapy:

For patients who are dosed initially at 75 mg/m^2 in combination with cisplatin, and whose nadir of platelet count during the previous course of therapy is < 25,000 cells/mm^3, in patients who experience febrile neutropenia, and in patients with serious non-hematologic toxicities, the dosage in subsequent cycles should be reduced to 65 mg/m^2. In patients who require a further dose reduction, a dose of 50 mg/m^2 is recommended.

Prostate Cancer:
Febrile neutropenia, neutrophils < 500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions or moderate neurosensory signs and/or symptoms during therapy ,Reduce dose to 60mg/ m^2.

Discontinue therapy if toxicities persist at lower doses.

Dose adjustment in hepatic impairment:
- In case of AST/ALT > 1.5 to ≤ 5 x ULN and AP > 5 to ≤ 5 x ULN, it should be reduced by 20%.
- In case of AST/ALT > 5 x ULN and/or AP > 5 x ULN it should be stopped.

Dose adjustment in renal impairment:
Docetaxel has minimal renal excretion. Dose adjustment may not be need.

Duration and number of cycles:
For the adjuvant treatment of operable node-positive breast cancer : every 3 weeks for 4-6 courses depending on protocol.

Contraindications:
Hypersensitivity to docetaxel or polysorbate 80
Solid tumor with baseline ANC<1500/mm^3
Bilirubin >ULN, AST or ALT >1.5 times ULN, alk phos >2.5 times ULN

Cautions:
Irritant
Treatment-related mortality higher in patients with hepatic impairment, those receiving higher doses, and in patients with NSCLC and history of prior platinum-based chemotherapy who receive docetaxel as a monotherapy at 100 mg/m^2.

Coadministration with CYP3A4 inhibitors may increase exposure to docetaxel and should be avoided; consider docetaxel dose reduction if unable to avoid.

Risk of severe fluid retention even with dexamethasone.

Unit price (MOH tenders):
Docetaxel vial 80 mg : 3607 ILS
Docetaxel vial 20 mg : 532 ILS

Stability:

Store intact vials at 2° C to 25° C . Protect from light . Solutions prepared from the one- vial should be used within 4 hrs of preparation .Solutions diluted for infusion in NS or D5W are stable for up to 4 weeks at room temp. in polyolefin containers; however, manufacturer recommends use within 4 hrs .

Epoetin alfa 2000 IU (prefilled syringe)

Indications

1. Anemia Due to Chronic Kidney Disease
2. Anemia in patients with non-myeloid malignancies where anemia is due to effect of concomitant myelosuppressive chemotherapy for >2 months

Level of prescriber: Nephrologist or internist Dose:

Chronic renal failure patients

1- Individualize dosing to achieve and maintain Hb between 10-12g/dl.
2- HB LEVEL SHOULD NEVER EXCEED 12g/dl.
3- children initial dose : 50units/ kg 3times/ week IV/Subcutaneous

Adult initial dose: 50-100unit/kg 3 times/week.

Chemotherapy-Related Anemia

Recommended starting dose: 150 units/kg IV or SC 3 times/week OR 40,000 units SC qWeek until completion of chemotherapy course
<5 yrs: Safety and efficacy not established
5-18 yrs: Recommended dose is 600 units/kg IV qWeek (not to exceed 40,000 U)
Concomitant DVT prophylaxis is recommended

Dose adjustment

1. decrease dose by 25% if Hb approaches 12g/dl or Hb increase > 1g/dl in 2 week period.
2. Initiate when the Hgb level is less than 10
3. If Hb continues to increase (by more than 1 g/dL in a 2-wk period) temporarily discontinue therapy until Hb begins to decrease then resume therapy with 25% reduction from previous dose.
4. increase dose by 25% if Hb < 10g/dl and does not increase by 1g/dl after 4 weeks of therapy.

5. if patient does not attain target Hb range after appropriate dose titration over 12 weeks . do not continue to increase dose and use the minimum effective dose that will maintain Hb level sufficient to avoid RBC transfusion.
6. IV route recommended for patients on hemodialysis

Follow up and monitoring in CRF

Prior the initiation of therapy:

1. Monitor BP :Blood pressure should be adequately controlled prior to initiation of therapy, and must be closely monitored and controlled during therapy.
2. Monitor Hb: The majority of patients with CKD will require supplemental iron during the course of therapy. Following initiation of therapy and after each dose adjustment, monitor hemoglobin weekly until the hemoglobin level is stable and sufficient to minimize the need for RBC transfusion.
3. Monitor transferrin saturation and ferritin. Transferrin saturation should be at least 20% and ferritin at least 100 ng/mL .May use supplemental iron if serum ferritin <100 mcg/L or serum transferrin saturation <20%

Unit price (MOH tenders): Epoetin alfa 2000 IU : 26 ILS

Cautions

- Not indicated for use in patients with cancer receiving biologic products, hormonal agents, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy;
- Increased mortality, MI, stroke, and thromboembolism: Using ESAs to target a hemoglobin level of greater than 12 g/dL increases the risk of serious adverse cardiovascular reactions .
- HTN, iron deficiency, folate or B12 deficiency, CHF, CAD, seizure disorder, sickle cell disease, hemolytic anemia, porphyria, hematologic disorder
- Cancer patients: Increased tumor progression rate when dosed to achieve Hgb >12 mg/dL so use the lowest dose needed to avoid red blood cell transfusion.

– Increased risk of seizures during first 90 days of therapy in CKD; monitor closely
– Dialysis patients: IV administration recommended to reduce red cell aplasia risk; may require increased anticoagulation with heparin to prevent clotting of extracorporeal circuit during hemodialysis
– only recommended during pregnancy when there are no alternatives and benefit outweighs risk.Caution be used when administered to nursing women.

Storage
Store at 2° to 8° C . Do not freeze or shake. Protect from light.
Single-dose: 1 mL vial contains no preservative. Use one dose per vial; do not re-enter the vial. Discard unused portions.

Stability at room temperature: Single-dose vial – 14 days

Darbepoetin alfa
CKD not on dialysis : Recommended starting dose: 0.45 mcg/kg IV/SC q4weeks

KD on dialysis
– Initiate ESA treatment when the hemoglobin level is <10 g/dL
– If the hemoglobin level approaches or exceeds 12 g/dL, reduce or interrupt the dose of ESA
– Recommended starting dose: 0.45 mcg/kg IV qWk or 0.75 mcg/kg IVq2wks

<1 year old: Safety and efficacy not established

1 yr old and older:
Not for initial use, indicated for conversion from epoetin alfa

Conversion from epoetin alfa

Previous Weekly Epoetin alfa	Aranesp Dose (mcg/week)	
Dose (Units/week)	**Adult**	**Pediatric**
1,500 >	6.25	Not established
to 2,499 1,500	6.25	6.25
to 4,999 2,500	12.5	10
to 10,999 5,000	25	20
to 17,999 11,000	40	40
to 33,999 18,000	60	60
to 89,999 34,000	100	100
90,000 ≤	200	200

- Reduce dose by 25% if rapid increase in Hgb (eg, >1 g/dL in 2-week period)
- Chemotherapy-Related Anemia with Nonmyeloid Malignancies

Adults:

2.25 mcg/kg SC qWeek OR 500 mcg SC q3Weeks

- If Hgb increases <1 g/dL after 6 weeks, may increase dose no > 4.5 mcg/kg
- Reduce dose by 40% if rapid increase in Hgb (eg, >1 g/dL in 2-week period)
- Discontinue if no response after 8 weeks
- Safety and efficacy not established to be used in pediatrics

Unit price (MOH tenders): Darbepoetin alfa : 56 ILS

Etanercept 25mg (vial or prefilled syringe)

Indications

1. Moderate to severe active rheumatoid arthritis not responding to traditional DEMARDS (or in combination) in adults
2. Moderately to severely active polyarticular juvenile idiopathic arthritis (JIA) not responding to traditional DEMARDS (or in combination).
3. Moderate to severe active Psoriatic Arthritis not responding to traditional DEMARDS (or in combination).
4. Active ankylosing spondylitis not responding to other medications.
5. Chronic moderate to severe plaque psoriasis not responding to traditional immunosuppressive drugs or DMARDS.

Level of prescriber

Etanercept should be prescribed by rheumatologist or dermatologist. The prescriber should write a report about the patient condition that necessitates its use. The report must contain information about the steps of management that precedes etanercept prescription and the report must be updated every 6 months.

Dose and dose adjustment.

- For subcutaneous use only. Must not inject >25 mg per injection site.
- In adults, methotrexate, glucocorticoids, salicylates, NSAIDs, and analgesics may be continued during treatment with etanercept. In juvenile idiopathic arthritis patients, glucocorticoids, NSAIDs, or analgesics may be continued during treatment with etanercept.
- Safety and efficacy not established in children younger than 2 y with juvenile idiopathic arthritis. Safety and efficacy in children with plaque psoriasis have not been established.

RA, Psoriatic arthritis and ankylosing spondylitis

50 mg once weekly or 25 mg twice weekly (individual doses should be separated by 72-96 hours).

Plaque psoriasis.

Initial : 50 mg twice weekly 3-4 days apart (starting dose of 25 or 50 mg once weekly have also been used successfully) ; maintain initial dose for 3 months

Maintenance dose: 50 mg once weekly.
Higher responses may be achieved from initial treatment for up to 12 weeks with a dose of 50 mg given twice weekly, after which, the dose should be reduced to the standard dose of 50 mg per week. If re-treatment with ENBREL is indicated, the dose used should be 50 mg per week.

Polyarticular juvenile idiopathic arthritis
- 0.8mg/kg once weekly max. 50mg weekly or 0.4mg/kg twice weekly.
- Max. 25mg twice weekly. (In most of the cases the children will not exceed the 25mg once weekly due to their low weight).

No special recommendations for dose adjustment.

In RA and plaque psoriasis , the treatment should ONLY be continued if the disease has improved sufficiently after 3 months. (The improvement will be seen in three ways functional, clinical, and radiographic).

In plaque psoriasis, psoriatic arthritis the treatment with Etanercept should continue until remission is achieved, for up to 24 weeks. (Assessment should be done)

Unit price (MOH tenders): Etanercept 25mg : 612 ILS

Storage and stability
- Must be refrigerated at 2° to 8° C
- Do not shake or freeze.
- Keep etanercept in the original carton and protected from light.

Acceptable Duration of Storage at Room Temperature:
Vial – seven days.

Prefilled syringe – four days

Contraindications:

1. Serious infection risk (Active TB , nvasive fungal infections, bacterial Legionella, Listeria), , and viral (hepatitis B , CMV)
2. Concurrent cyclophosphamide therapy or patients with Wegener granulomatosis receiving immunosuppressive therapy
3. Hypersensitivity
4. Concomitant use of live vaccines

Cautions:

– CHF, HBV-positive status, history of or susceptibility to recurring infections, history of blood dyscrasias
– Monitor closely for signs or symptoms of demyelinating disease (eg, confusion, numbness, vision changes)
– Increased risk of lymphoma and TB; monitor for TB
– Possibility of lupuslike symptoms; discontinue if such symptoms develop
– Consider discontinuing if hematologic disorders (eg, pancytopenia, leukopenia, thrombocytopenia, aplastic anemia) occur
– Diluent for multidose vial contains benzyl alcohol as preservative
– Children should be up to date with immunizations before starting drug
– Increased risk of lymphoma and other cancers reported in children and adolescents
– Occurrence of leukemia and new-onset psoriasis reported in patients treated with TNF blockers

Follow up and monitoring

1. Purified Protein Derivation (PPD) prior to therapy initiation and periodically during therapy. If positive treat for TB then start etanercept
2. Discontinue if patient develop of serious infections or sepsis.
3. Consider periodic skin examinations for all patients at increased risk for skin cancer.
4. Monitor all patients for exacerbation or new-onset of CHF.

Esomeprazole sodium IV Inj: 40mg

INDICATIONS

1. Prevention of recurrent GI bleeding following endoscopy in patients with confirmed active gastric or duodenal ulcer in high-risk patients after obtaining initial hemostasis.
2. Short-term treatment of gastroesophageal reflux disease with erosive esophagitis when oral medication is not possible or inappropriate.

Level of prescriber : All use must be approved by Gastroenterologist /GI surgeon.

GUIDELINES FOR USE –

Candidates for IV esomeprazole are patients with high-risk bleeding peptic ulcers and patients with erosive esophagitis who cannot tolerate oral medications.

ADULT DOSAGE & DURATION

Prevention of recurrent GI bleeding:

Esomeprazole within 24 hours of the procedure as 80 mg IV bolus over 30 minutes, followed by 8 mg/hr infusion for up to 72 hours. THEN Continue healing dose of proton pump inhibitor orally for 8 weeks. First line is omeprazole 40mg daily.

If patients continue to be NPO after 72 hours, then the esomeprazole continuous infusion should be converted to esomeprazole 40 mg IV Push once daily up to 7 days..

Treatment of erosive esophagitis:

Adult : 20 mg or 40 mg qd IV inj (no less than 3 min) or infusion (10-30 min). Up to 10 days.
Switch to PO once patient able to swallow

1 to 17 yr : IV 10 mg (wt < 55 kg) or 20 mg (wt ≥ 55 kg) once daily
1 mo to < 1 yr : IV 0.5 mg/kg once daily.

Dosage adjustment
No dosage adjustment is necessary in elderly, renal or hepatic impairment
For patients with severe liver impairment (Child Pugh Class C), a dose of 20 mg should not be exceeded
The manufacturer recommends that children receive IV esomeprazole by intermittent infusion only
Use esomeprazole in pregnancy only if the potential benefit outweighs the risk to fetus

Lactation : discontinue breastfeeding or discontinue the drug

Unit price (MOH tenders):
Esomeprazole sodium IV Inj: 29 ILS

Storage: to 15-30°C .
Protect from light.

Reconstituted Sol: (up to 30°C) use within 12 hrs after reconstitution with NS or LR or within 6 hours after reconstitution with D5W.

Cautions
- increased incidence of Clostridium difficile-associated diarrhea (CDAD) .
- PPIs may decrease efficacy of clopidogrel by reducing the formation of the active metabolite
- Gastric atrophy reported with long-term use of another PPI
- Severe hepatic impairment
- Relief of symptoms does not eliminate the possibility of a gastric malignancy
- Therapy increases risk of Salmonella, Campylobacter, and other infections

- Contains enteric coated granules (acid labile); do not chew or crush; take 1 hr before meals
- increased risk for osteoporosis-related fractures of the hip, wrist, or spine; particularly with prolonged (>1 yr), high-dose therapy
- Hypomagnesemia may occur with prolonged use (ie, >1 yr); adverse effects may result and include tetany, arrhythmias, and seizures; and PPI had to be discontinued

Filgrastim Injection: 300 mcg/0.5ml

Indications:

1. Cancer Patients Receiving Myelosuppressive Chemotherapy associated with a significant incidence of severe neutropenia
2. Patients With Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of adults with AML.
3. Cancer Patients Receiving Bone Marrow Transplant is indicated to reduce the duration of neutropenia
4. Patients With Severe Chronic Neutropenia

Level of prescriber: Oncologists. Hematologist .Internal physician

Dose and dose adjustment

Cancer Patients Receiving Myelosuppressive Chemotherapy:

– The recommended starting dose of filgrastim is 5 mcg/kg/day, as single daily injection by subcutaneous bolus, by short (15 to 30 min) IV infusion, or by continuous subcutaneous or IV infusion daily for up to 2 wk until ANC reaches 10,000/mm ^{3}
– Doses may be increased in increments of 5 mcg/kg for each chemotherapy cycle ,according to the duration and severity of ANC nadir.
– Filgrastim should be administered no earlier than 24 hours after the administration of cytotoxic chemotherapy. Filgrastim should not be administered in the period 24 hours before the administration of chemotherapy.
– Filgrastim should be administered daily for up to 2 weeks or until the ANC has reached 10,000/mm^3 . Discontinue if the ANC surpasses 10,000/mm ^{3} .
– Patients with Acute Myeloid Leukemia Receiving Induction Chemotherapy
– Filgrastim at a dose of 5mcg/kg/day after last dose of chemotherapy until neutropenia recovery.

Patients with Severe Chronic Neutropenia:
Starting Dose: Congenital Neutropenia: The recommended daily starting dose is 6 mcg/kg BID SC every day. Adjust the dose based on ANC and clinical response.

Idiopathic or Cyclic Neutropenia: The recommended daily starting dose is 5 mcg/kg as a single injection SC every day.

Bone marrow transplantation: IV/Subcutaneous 10 mcg/kg/day. Adjust the dose according to the duration and severity of neutropenia.

Dose Adjustments: No data available in hepatic or renal impairment
Unit price (MOH tenders): Filgrastim Injection: 395 ILS

Storage and Stability
- Prefilled syringe should be stored in the refrigerator at 2° to 8°C
- Avoid shaking. Should be protected from freezing & temp > 30° to avoid aggregations
- Prior to injection, it may be allowed to reach RTemp for a maximum of 24 hrs.

Cautions :
- Associated with rare cases of potentially fatal splenic rupture; evaluate if patient experiences left upper abdominal and/or shoulder tip pain
- Rare cases of acute respiratory distress syndrome reported
- Monitor for thrombocytopenia

Follow up and monitoring.
- In Cancer Patients Receiving Myelosuppressive Chemotherapy a CBC with differential should be obtained before instituting filgrastim therapy, and monitored twice weekly during therapy.
- CBC with differential and platelet count three times a week following bone marrow transplantation.
- For severe chronic neutropenia monitor CBC with differential and platelet count twice weekly during the first month of therapy and for two we following dose adjustment and monthly for first year then at least quarterly thereafter.

Goserelin 3.6 mg syringe

Indications

1. Advanced Prostate cancer
2. Advanced Breast cancer in pre and perimenopausal woman Palliative treatment of advanced breast cancer in pre- and perimenopausal women.The estrogen and progesterone receptor values may help to predict whether Zoladex therapy is likely to be beneficial
3. Endometriosis
4. Endometrial thinning.

Level of prescriber

Goserelin should be prescribed by oncologist or gynecologist .The prescriber should write a report about the patient condition that necessitates its use. The report should be updated every six months for indications that need more than six months of treatment.

Dose and dose adjustment

Prostatic Carcinoma 3.6 mg injected SQ into the anterior abdominal wall every 28 days or 10.8 on day 1, repeat cycle every 12 weeks (3 months)

Advanced Breast cancer : 3.6 mg every 28 days

Endometriosis: 3.6 mg every 28 days for 6 months. Experience has been limited to women 18 years of age and older .

Endometrial thinning prior to endometrial ablation for dysfunctional uterine bleeding: 3.6 mg every 28 days for 1 or 2 doses.

Uterine fibroids when previous heavy menstrual loss has caused anaemia : 3.6 mg every 28 days

Dose adjustment in hepatic impairment: No adjustment is necessary with moderate impairment; no data for severe impairment.

Duration: 6 months (endometriosis), long term in prostate and breast cancer.

Contraindications
Pregnancy (for endometriosis), lactation, undiagnosed abnormal vaginal bleeding

Cautions :
- Manifestations of disease may worsen at beginning of therapy
- Avoid pregnancy; premenopausal women should use nonhormonal contraception until >12 wk following end of treatment
- Males at risk of ureteral obstruction or spinal compression
- Ongoing analysis found that men receiving GnRH agonists for prostate cancer were at a small increased risk for diabetes, heart attack, stroke, and sudden death
- Do not exceed 6 month treatment duration with GnRH angonists in women (except when treating breast cancer) because of possible osteoporotic effects.

Unit price (MOH tenders):
Goserelin 3.6 mg syringe : 545 ILS
Storage and Stability
Should be stored at room temperature, not to exceed 25 C. Protect from light.

Follow up and monitoring
Bone mineral density, serum calcium, and lipid.
Prostate cancer: urinary tract obstruction in 1st few weeks, screen for diabetes.

Imatinib 400mg tablet

Indications:

1- Newly diagnosed adult and pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia (CML) in chronic phase & in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy for adult.

2- Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST) & Adjuvant treatment of adult patients following complete gross resection of Kit (CD117) positive GIST

3- Ph+ ALL Adult patients

Level of prescriber

Imatinib should be prescribed by Hematologist or Oncologist.
The prescriber should write a report about the patient condition that necessitates its use. The report should be updated every six months.

Dose and dose adjustment

Patients with Ph+ CML CP, AP and BC-1(chronic phase + accelerated phase +blast phase):

- 400 mg/day for adult patients in chronic phase CML and 600 mg/day for adult patients in accelerated phase or blast crisis.

- In CML, a dose increase from 400 mg to 600 mg in adult patients with chronic phase disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in adult patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-leukemia related Neutropenia or thrombocytopenia in the following circumstances:

[Disease progression (at any time), failure to achieve a satisfactory hematologic response after at least 3 months of treatment, failure to achieve a cytogenetic response after 6-12 months of treatment, or loss of a previously achieved hematologic or cytogenetic response].

- Children > 2 years: 340 mg/m^2/day PO; not to exceed 600 mg/day

GIST patients:
400 mg/day for adult patients with unresectable and/or metastatic, malignant GIST. A dose increase up to 800 mg daily may be considered, as clinically indicated, in patients showing clear signs or symptoms of disease progression at a lower dose and in the absence of severe adverse drug reactions.
Adjuvant treatment: the recommended dose is 400 mg/day.
Ph+ ALL: Adults PO 600 mg/d.

Dose adjustment
1) Concomitant Strong CYP3A4 inducers
The use of concomitant strong CYP3A4 inducers (eg, carbamazepine, dexamethasone, phenobarbital, phenytoin, rifabutin, rifampin). should be avoided, If patients must be co-administered the dosage should be increased by at least 50%, and clinical response should be carefully monitored
2) Hepatic Impairment
– Mild and moderate hepatic impairment do not require a dose adjustment.
– Severe hepatic impairment 25% decrease in the recommended dose.
– elevations in bilirubin > 3 x institutional upper limit of normal (IULN) or in liver transaminases > 5 x IULN occur, it should be withheld until bilirubin levels have returned to a < 1.5 x IULN
3) Renal Impairment
– Moderate renal impairment :(CrCL = 20-39 mL/min) 50% decrease in the recommended starting dose a by 50% nd future doses can be increased as tolerated & doses greater than 400 mg are not recommended.
– Mild renal impairment (CrCL = 40-59 mL/min): Doses greater than 600 mg are not recommended .
– severe renal impairment (CrCl less than 20 mL/min) : use is not recommended.

Hematologic toxicity

- Generally, discontinue if ANC <1000/mm^3 and/or Plts <50,000/mm^3
- Resume when ANC >1500/mm^3 and Plts >75,000/mm^3

Duration of treatment: Treatment may be continued as long as there is no evidence of progressive disease or unacceptable toxicity

Unit price (MOH tenders):
Imatinib 400mg tablet: (TH) 393770 ILS

Special precautions for storage
- Not store above 30°C.
- Protect from moisture.
- Store in the original package.

Follow up:

Efficacy: in CML baseline molecular and cytogenetic assessment. BCR-ABL transcripts should be evaluated by RT-PCR every 3 months and bone marrow cytogenetic performed at 6 _12 months following the start of therapy.
If a patient develops an increase in BCR-ABL transcripts: assess patient adherence, repeat BCR-ABL in 1 to 3 months for patients with a prior major molecular response.

Others:

1- CBC weekly for first month, twice weekly for 2nd month then periodically (every 2-3 month).
2- LFT (baseline and monthly or as clinically indicated; more frequently (at least weekly) in patients with moderate to severe hepatic impairment, monitor patient need for dose adjustment.
3- Baseline KFT. Monitor patient need for dose adjustment.
4- Serum electrolytes.

5- Thyroid function test (in thyroidectomy patients).

6- Monitor for signs and symptoms of CHF in patients at risk or pre existing cardiac disease..

Precautions:

1) Fluid Retention and Edema

2) Hematologic Toxicity

3) Severe Congestive Heart Failure and Left Ventricular Dysfunction

4) Hepatotoxicity & Dermatologic Toxicities

5) Gastrointestinal Disorders

6) Hypereosinophilic Cardiac Toxicity & Hemorrhage If anticoagulation required, use LMW or standard heparin instead of warfarin

7) Toxicities from Long-Term Use:

Growth retardation may occur in children and adolescents

Immune Globulin IV 5g 100ml

Indications:

1. Primary Immunodeficiency Diseases (PID): congenital agammaglobulinemia, common variable immunodeficiency,X-linked immunodeficiency, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies syndromes(SCIDS).
2. Immune thrombocytopenic purpura(ITP).
3. Chronic inflammatory demyelinating polyneuropathy(CIDP)as an alternative to plasma exchange.
4. Guillian–Barré Syndrome (GBS)
5. Kawasaki Disease
6. Myasthenia Gravis (MG)
7. B-cell Chronic Lymphocytic Leukemia (CLL)

Level of prescriber

Immune Globuline should be prescribed by Pediatrics, Neurologist, and Hematologists, Internist.

Dosage & Duration of Treatment:

- The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.
- Approved doses & regimens may vary between brands, check manufacture guidelines.

Primary Immunodeficiency Diseases (PID):

Adults and Children :

300-600 mg/kg every 3 to 4 weeks based on clinical response.

Immune thrombocytopenic purpura (ITP):

Refractory acute ITP :

- Initial therapy: up to 2 g/kg total dose, generally given as 2 doses of 1 g/kg
- Ongoing therapy when indicated: 1–2 g/kg in single or divided dose at

4 to 6 weekly intervals titrated to symptoms and platelet count.
- Further doses may be administered in responsive patients for up to 6 months

Chronic inflammatory demyelinating polyneuropathy(CIDP):
- Loading Dose: 2000mg\Kg divided over 2-4 days. Maintenance:1000mg\Kg\day for 1 day every 3 weeks or 500 mg\Kg\day for 2 days every 3 weeks.
- Assessment: every 3 months for chronic progressive disease to determine if there is response. If there is no response discontinue IVIG.
- Guillian–Barré Syndrome (GBS) : IVIG 0.4 g/kg/day for 5 days.

Kawasaki disease:
- IVIG 2 g \ Kg in a single dose with a high dose of aspirin (80-100 mg/kg/d).
- Early in Kawasaki disease 2 g/kg in a single dose over 10–12 hours unless cardiac function necessitates the administration of a prolonged or divided treatment dose.

Myasthenia Gravis (MG) (Off- label)
IVIG dose is 2,000 mg/kg given over 2 to 5 days.
NOTE: Evidence does not support the use of IVIG maintenance therapy for Myasthenia gravis.

B-cell chronic lymphocytic leukemia CLL:
- 400mg\Kg\dose every 3-4 weeks.
- Six-monthly review to assess clinical benefit.
- Unit price (MOH tenders): Immune Globulin IV 5g 100ml: 1104 ILS

Dose adjustment in renal impairment:
- Avoid use in pt. CrCl<10 ml/min.
- In pt. at risk of renal dysfunction, consider infusion at a rate less than maximum.

Storage & Stability:
Stability is dependent upon the manufacturer& brand. Don't freeze.

Cautions :

1. Postpone live virus vaccines for at least 3 months
2. Associated with various renal dysfunctions, incl ARF (especially those containing sucrose but not with the D-sorbitol–stabilized formulation.); monitor renal function
3. Transfusion-Related Acute Lung Injury (TRALI)
4. Thrombosis may occur even in absence of known risk factors. For patients at risk of thrombosis, administer at the minimum concentration available and at the minimum rate of infusion practicable
5. Maltose-containing brands may give false high for glucose in certain glucose-testing systems
6. Hemolytic anemia can develop

Monitoring:

- Renal function ,urine output(adequate hydration prior to the initiation of infusion IVIG is required).
- Hemoglobin, hematocrit ,platelets in ITP pts.
- Infusion related IV reactions.
- Hemolysis & increasing of blood viscosity.
- Thromboembolic events, including myocardial infarction.

Interferon beta -1 a

Indications:
Treatment of relapsing forms of multiple sclerosis (MS)

Prescriber &Specialty:
Should be prescribed by Neurologist. The prescriber should write a report about the patient condition that necessitates its use. The report should be updated every six months .

Dose &dose adjustment:
There are two different brands:
A) Interferon beta -1a 30 mcg (Avonex) I.M: Prefilled syringe 30 mcg per 0.5 mL

1) 30 mcg once weekly
2) Recommendation by FDA is gradually-increasing dosing schedule for people starting the medication as follows:
   - Week 1 7.5 micrograms (1/ 4 dose)
   - Week 2 15 micrograms (1/ 2 dose)
   - Week 3 22.5 micrograms (3/ 4 dose)
   - Week 4 and following full dose

Dose adjustment: No data about dose adjustment

B) Interferon beta -1a 44 mcg (Rebif) SubQ : Prefilled syringe
Patients should be started at 20% of the prescribed dose three times per week and increased over a 4-week period to the targeted dose as the following:

Week 1 Titration·	8.8 mcg
Week 2 Titration·	8.8 mcg
Week 3 Titration·	22 mcg
Week 4 Titration·	22 mcg
Week 5 and on·	44 mcg

Rebif should be administered, if possible, at same time (preferably in late afternoon or evening) on the same 3 days each wk, at least 48 hours apart each wk.

Dose adjustment:
If liver function tests increase or increase of leukopenia : decrease dose 20%-50% until toxicity resolves

Stability:
- Stable at 2- 8°C .
- Do not freeze.If a refrigerator is not available, unopened vials, but not prefilled syringes, may be stored at temperatures at or less than 25°C for up to 30 days, away from heat and light. Once warmed to room temperature, prefilled syringe must be used within 12 h.

Children: Safety and efficacy in younger than 18 yr of age not established.

Follow up
Efficacy :
1) Comparing Number of relapse .
2) Annual MRI .
3) If no response (clinically & MRI) discontinue & change to other treatment.

Duration: Most of clinical trials were conducted for 2 years.

Unit price (MOH tenders):
- Interferon beta -1a 30 mcg (Avonex): 504 ILS
- Interferon beta -1a 44 mcg (Rebif): 243 ILS

Warning & precautions:

- Depression, Suicide, and Psychotic Disorders (avoid use in patient with sever psychiatric disorder)
- Hepatic Injury (avoid in liver cirrhosis)
- Anaphylaxis and Other Allergic-Reactions
- Congestive Heart Failure
- Decreased Peripheral Blood Counts
- Seizures
- Autoimmune Disorders

Monitor

- Hgb, CBC with differential, platelet count, and blood chemistries, including LFTs, are performed before initiating therapy, at 1, 3, and 6 mo after starting therapy, and then periodically thereafter.
- Thyroid function tests are performed before starting therapy and every 6 mo during therapy in patients with thyroid dysfunction.

Meropenem 1gm vial

Carbapenem

INDICATIONS

1. Treatment of intra-abdominal infections (complicated appendicitis and peritonitis caused by viridans group streptococci, E.coli, Klebsiella pneumoniae, P. aeruginosa , Bacteroides fragilis, B. thetaiotaomicron, and Peptostreptococcus species.)
2. bacterial meningitis : caused by Streptococcus pneumoniae , H. influenzae (β-lactamase- and non-β-lactamase-producing isolates), and Neisseria meningitidis.
   The efficacy of Meropenem as monotherapy in treatment of meningitis caused by penicillin nonsusceptible isolates of Streptococcus pneumoniae has not been established.
3. complicated skin and skin structure infections (Staph. aureus (β-lactamase- and non-β-lactamase-producing, methicillin-susceptible isolates only), Streptococcus pyogenes, Streptococcus agalactiae, viridans group streptococci, Enterococcus faecalis (excluding vancomycin-resistant isolates), Pseudomonas aeruginosa, E. coli, Proteus mirabilis, Bacteroides fragilis, and Peptostreptococcus species.)

   Meropenem active against most gram-negative (including multidrug-resistant), grampositive (including E. faecalis), anaerobes

Weaknesses: Stenotrophomonas, Pseudomonas aeruginosa (development of resistance over time), methicillin-resistant staphylococci, E. faecium, C. difficile

General Guidelines:

– Meropenem prescribed only for hospitalized patients (severely ill patients) .
– Samples for culture and antibiotic sensitivity (C/S) must be sent to laboratory before starting antibiotic therapy.
– If the result of C/S showed sensitivity to less spectrum antibiotic ,

meropenem should be changed to less spectrum antibiotic (cost effectiveness should be considered).

- Use for the shortest duration possible that gives an appropriate clinical outcome for each condition.
- The prescription of meropenem should be restricted to specialist only to avoid abuse and development of multi-resistant strains & after duty hours, attending physician can prescribe meropenem for up to 24 hours and after that the order should be countersigned by specialist mentioning his name.
- A report of patient condition &culture sensitivity report should be made available in the pharmacy within 72 hours or else the pharmacy will stop dispensing unless continuation is justified.

Dosage and duration of treatment:

- Administered by intravenous infusion over approximately 15 to 30 minutes. Doses of 1 g may also be administered as an IV bolus injection (5 to 20 mL) over approximately 3-5 minutes.

Usual Adult Dose for Intraabdominal Infection

1 g IV every 8 hours for 7 to 14 days.

Usual Adult Dose for Meningitis

1 to 2 g IV every 8 hours for 7 to 21 days depends on causative organisms.

Usual Adult Dose for Nosocomial Pneumonia

1 g IV every 8 hours

Initial empiric treatment with broad-spectrum coverage according to the hospital's and/or ICU's antibiogram is recommended if multidrug-resistant organisms are suspected.

Duration: If the causative organism is not Pseudomonas aeruginosa, the duration of treatment should be as short as clinically possible (8 days) to reduce the risk of super infections with resistant organisms.

Usual Adult Dose for Skin or Soft Tissue Infection
Complicated infection: 500 mg IV every 8 hours

Duration:
Therapy should generally be continued for ~ 7 to 10 days, or for 3 days after the acute inflammation disappears, depending on the nature and severity of the infection. For more severe infections, such as diabetic soft tissue infections, 14 days of therapy may be required.

Dosage Schedule for Pediatrics (≥ 3 Months only) with Normal Renal Function

Type of Infection	Dose (mg/kg)	Up to Maximum Dose (≥ 50 kg)	Dosing Interval
Complicated skin and skin structure	10	500 mg	Every 8 hours
Intra-abdominal	20	1 g	Every 8 hours
Meningitis	40	2 g	Every 8 hours

There is no experience in pediatric patients with renal impairment.

Contraindications
- Hypersensitivity to meropenem, or other carbapenems
- Patients who have experienced anaphylactic reactions to other beta-lactams

Cautions
- Seizures have been reported, most commonly in patients with CNS disorders (eg, brain lesions, history of seizures) or with bacterial meningitis or compromised renal function. Seizures, headaches, or paresthesias may occur, potentially interfering with mental alertness or causing motor impairment
- Clostridium difficile-associated diarrhea has been reported

- To avoid resistance, drug should be used only in proven or strongly suspected bacterial infections
- Prolonged use may result in overgrowth of nonsusceptible organisms
- Thrombocytopenia has been reported in patients with renal impairment
- Meropenem should only be given during pregnancy when need has clearly been established.
- caution should be used when administering meropenem to nursing women.

Unit price (MOH tenders):
Meropenem 1gm vial: 97 ILS

Renal Dose Adjustments
Adults:
CrCl 26 to 50 mL/min: Usual dose every 12 hours
CrCl 10 to 25 mL/min: One-half recommended dose every 12 hours
CrCl 9 mL/min or less: One-half recommended dose every 24 hours
Liver impairment dose adjustments: No adjustment recommended

MONITORING
Monitor for signs/symptoms of anaphylactic/ hypersensitivity reactions, CDAD, superinfections, and seizures. Periodically monitor organ system functions (eg, renal, hepatic, hematopoietic) during prolonged use.

ADMINISTRATION/STORAGE
Administration: IV route.
Storage: Dry Powder: 20-25°C .

Compatibility and Stability
Meropenem should not be mixed with or physically added to solutions containing other drugs.
Solutions of meropenem should not be frozen.
Intravenous Bolus Administration

Meropenem injection vials constituted with sterile water may be stored for up to 2 hours at room temperature 15-25°C or for up to 12 hours at 4°C .

Intravenous Infusion Administration
Meropenem) infusion vials constituted with Sodium Chloride Injection 0.9% are stable for up to 2 hours at room temperature 15-25°C or for up to 18 hours at 4°C .

Infusion vials of meropenem constituted with Dextrose Injection 5% are stable for up to 1 hour at room temperature 15-25°C or for up to 8 hours at 4°C.

Octreotide ampoule: 0.1 mg/ ml
Octreotide depot (LAR): 20 mg VIAL

Indications:

1. Control of symptoms (flushing and diarrhea) associated with metastatic carcinoid tumors .
2. Treatment of watery diarrhea associated with vasoactive intestinal peptide-secreting tumors (VIPomas).
   A high-quality randomized controlled trial shows that ranitidine plus dexamethasone can achieve same benefits as octreotide, but at a much lower cost. Ranitidine (200 mg over 24 hours), dexamethasone (8 mg over 24 hours), and hydration (10 to 20 mL/kg over 24 hours) — all delivered as either a bolus or subcutaneous continuous infusion.
3. Acromegaly
4. Emergency management to stop bleeding and to protect from re-bleeding owing to gastroesophageal varices in patients with cirrhosis.

Level of prescriber: Oncology, endocrinologist, Internist.

Dose:

Carcinoid Tumors:
S.C.,I.V.: the first 2 weeks of therapy ranges from 100-600 mcg/day in 2-4 divided doses (mean daily dosage is 300 mcg).
I.M. depot injection: Patients must be stabilized on s.c. Octreotide for at least 2 weeks before switching to the long acting depot. Upon switch: 20 mg I.M. intragluteally every 4 weeks for 2 months.

VIPomas:
S.C.,I.V.: initial 2 weeks: 200-300 mcg\day in 2-4 divided doses (range 150-750 mcg) to control symptoms of the disease. On an individual basis, dosage may be adjusted to achieve a therapeutic response, but usually doses above 450 mcg/day are not required.

I.M. depot injection:
Patients must be stabilized on s.c. Octreotide for at least 2 weeks before switching to the long acting depot. Upon switch: 20 mg I.M. intragluteally every 4 weeks for 2 months, then the dose may be modified based upon response.

Acromegaly:
S.C.,I.V.:
50 mcg 3 times/day, titrate to achieve growth hormone levels less than 5 ng/mL or IGF-I (somatomedin C) levels less than 1.9 U/mL in males and less than 2.2 U/mL in females. Usual effective dose 100 – 200 mcg 3 times/day, range: 300-1500 mcg/day.

I.M. depot injection: Patients must be stabilized on s.c. Octreotide for at least 2 weeks before switching to the long acting depot. Upon switch: 20 mg I.M. intragluteally every 4 weeks for 3 months, then titrate the dose as follows :

- Symptoms controlled: If GH < 1 ng/mL and IGF-1 normal, decrease dose to 10 mg IM every 4 weeks; if GH < 2.5 ng/mL and IGF-1 normal, maintain dose at 20 mg IM every 4 weeks
- Symptoms uncontrolled: If GH > 2.5 ng/mL or IGF-I elevated, increase dose to 30 mg IM every 4 weeks; if symptoms persist, increase to 40 mg IM

Octreotide should be withdrawn yearly for a 4 weeks interval in patients who have received irradiation.

Esophageal varices bleeding:
I.V. bolus 25-50 mcg followed by continues i.v. infusion of 25-50 mcg/ hour for 1-5 days .

Duration:
12 months is the typical period in carcinoid tuomor & VIPomase.
long-term treatment in acromegaly.

Important Limitations of Use
In patients with carcinoid syndrome and VIPomas, the effect of Sandostatin Injection and Sandostatin LAR Depot on tumor size, rate of growth and development of metastases, has not been determined.

Unit price (MOH tenders):
Octreotide ampoule: 500 ILS
Octreotide depot (LAR): 5752 ILS

Stability:
Octerotide should be stored at refrigerated temperatures 2°C-8°C. Protect from light. At room temperature, (20°C-30°C), Sandostatin is stable for 14 days if protected from light. The solution can be allowed to come to room temperature prior to administration. Do not warm artificially. Stable for up 7 days in a polypropylene syringe.

Cautions & Follow up
- Carcinoid: 5-HIAA , plasma serotonin, and plasma substance P.
- VIPomase: vasoactive intestinal peptide.
- Acromegaly: growth hormone, somatomedin C (IGF-1).
- zinc level (patients with excessive fluid loss maintained on TPN).
- May alter fat absorption in some patients (monitor for pancreatitis)
- May decrease vitamin B12 levels (monitor)
- Monitor for hypothyroidism (octreotide suppresses secretion of TSH)
- Use caution when giving drug to patients with cardiovascular
- disease may enhance toxicity of QT-prolonging agents
- Do not use depot formulation in patients with sulfonylurea-induced hypoglycemia

Onabotulinum toxin A 100 IU

Indications
1-Treatment of adults (≥ 16 yrs) with cervical dystonia.
2- Dynamic muscle contracture in pediatric cerebral palsy patient's ≥ 2 years
(off label use).

Level of prescriber
The drug should be prescribed by a neurologist; the prescriber should write a report about the patient condition that necessitates its prescription. The report should be updated every 6 months if the patient needs retreatment.

Dose and dose adjustment.
Cervical dystonia: ≥16 yr
- The mean dose is 198- 300 units divided among the affected muscles
- The initial dose should be lower in previously untreated patients.
- The dose injected into the sternocleeidomastoid muscle should be ≤ 100 units
- Patients may require retreatment every 3 months. After assessment of the patient clinical condition
- Clinical improvement generally begins within the first two weeks after injection with maximum clinical benefit at approximately six weeks post-injection.
  But it can become ineffective after a time

Cerebral palsy
For children ≥ 2 years:
IM 4 units/kg (total dose) divided into two injections into medial and lateral heads of the gastrocnemius of affected limb . maximum dose is 200 units.

Each small muscle receives 1-2 U/kg, and large muscles, 4-6 U/kg. The interval between doses should be at least 4 months in order to help prevent

antibody formation, which could make subsequent botulinum toxin procedures less effective. Note that large muscles may not respond to this limiting dose, or quite often, patients need several muscles done at each visit. Treatment may be repeated every 2 months after assessment of the patient clinical condition.

Dose adjustment
No specific adjustment is recommended in renal or hepatic impairment. Safety and efficacy not established in < 12 years old child

Storage/Stability
Store unopened vials in refrigerator (2° to 8°C) for up to 24 months. Reconstituted solution may be stored for up to 24 h if refrigerated. Do not freeze reconstituted solution. Discard any remaining solution

Contraindications:
Hypersensitivity , Neuromuscular disease, Infection at the proposed injection site, Intradetrusor injection: Urinary tract infection or urinary retention (post-void residual >200 mL)

Cautions:
- Risk of respiratory compromise & death esp in children treated for cerebral palsy-associated spasticity
- Effects of the botulinum toxin may spread from the area of injection to other areas of the body, causing symptoms similar to those of botulism - watch for dyspnea, dysphagia or speech impairment
- The different botulinum toxin products are not interchangeable
- Pre-existing neuromuscular disorders.

Unit price (MOH tenders): OnabotulinumtoxinA 100 IU : 1200 ILS
Follow up and monitoring
1- Use the appropriate gauge needle according to the muscle depth.
2- Use is contraindicated if infection is present at the injection site.

Rituximab 500mg/50ml vial & 100mg/10ml

Indication:

1) Non–Hodgkin's Lymphoma (NHL): Relapsed or refractory, low-grade or follicular, CD20-positive before starting treatment, B-cell NHL.
2) Chronic Lymphocytic Leukemia (CLL): CD20-positive before starting treatment.
3) Rheumatoid Arthritis: severe active rheumatoid arthritis who have an inadequate response to or intolerance of other (DMARDs) ,and not responding to one or more TNF antagonist.
   Data suggest that seropositivity for the autoantibodies rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) may confer improved clinical benefit compared with patients negative for both.

Level of prescriber

Rituximab should be prescribed by Hematologist or Rheumatologist.
The prescriber should write a report about the patient condition that necessitates its use. The report should be updated every six months for indications that need more than six months of treatment.

Dose: Adults

Non-Hodgkin's Lymphoma (NHL): according to following schedules

- Relapsed or refractory low-grade or follicular, CD20-positive, B-cell NHL: Once wkly x4-8 doses
- Retreatment for relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL: Once weekly x4 doses
- Previously untreated, follicular, CD20-positive, B-cell NHL: Administer on Day 1 of each chemotherapy cycle for up to 8 doses; with complete or partial response, initiate maintenance 8 weeks following completion of combination chemotherapy as a single-agent q8weeks for 12 doses
- Diffuse large B-cell NHL: Administer on Day 1 of each cycle of che-

motherapy for up to 8 infusions

Untreated and previously treated CD20-positive Chronic Lymphocytic Leukemia (CLL):

– 375 mg/m^2 IV infusion on day 1 of 1st cycle (for 1st cycle, administer 1 day before chemotherapy with FC), THEN
– 500 mg/m^2 IV on day 1 of subsequent cycles (administer on same day as chemotherapy with FC)

Repeat q28 days x6 cycles

Rheumatoid Arthritis (RA): 1000 mg on day 1 and 15 in combination with methotrexate. (for up to 6 months).

Premedicate with glucocorticoids 30 minutes before infusion to reduce infusion rxn .

Treatment with rituximab plus methotrexate should be continued only if there is an adequate response following initiation of therapy.

An adequate response is defined as an improvement in disease activity score (DAS 28) of 1.2 points or more. Repeat courses of treatment with rituximab plus methotrexate should be given no more frequently than every 6 month

Cautions

– Cardiac arrhythmia, angina, high tumor burden, concomitant cisplatin
– Infusion reactions may occur and are potentially fatal; reactions may resolve with slowing or suspending infusion; risk diminishes with subsequent infusions
– Risk of potentially fatal mucocutaneous reactions
– Risk of potentially fatal tumor lysis syndrome
– Increased risk of potentially fatal hepatitis B virus reactivation
– Potential risk of progressive multifocal leukoencephalopathy

Follow up

1- CBC with differential and platelets at weekly to monthly intervals and more frequently in patients who develop cytopenias.
2- KFT , fluid balance and vital signs
3-Cardiac monitoring in RA patients and in patients with preexisting cardiac disease.

4- Screen for hepatitis B and hepatitis C in high risk patients

Monitoring parameters:

Start of therapy

1- CD20 positive for NHL and CLL patients

2- Rheumatoid factor (RF) (anti-CCP) seropositive for RA patients

Unit price (MOH tenders):

Rituximab 500 mg /50ml vial: 10917 ILS

Rituximab 100mg/10ml: 2241 ILS

Stability:

Rituximab solutions for infusion may be stored at 2°C-8°C for 24 hours. Rituximab solutions for infusion have been shown to be stable for an additional 24 hours at room temperature.

Surfactant 6 ml & 3 ml vial

Indications:

1. Treatment of Respiratory Distress Syndrome (RDS) in premature infants. Surfactants have been usually used for treating infants at 2 to 72 hours of age after a (confirmed by clinical and radiologic findings) and requiring endotracheal intubation.
2. Surfactants can be used for extremely premature neonates from 27 weeks' gestation until before 34 weeks.
3. Prophylactic use of surfactant in babies at high risk of developing RDS does not lead to clinical improvement and may increase the risk of lung injury (lung hemorrhage and patent ductus arteriosus) or death.

Dose and duration:

Usual Dose:

3mL/kg body weight at birth. Administer every 12 hrs. Max: 3 doses.

Re-treatment with surfactant should be flexible and determined by the baby's condition. It would be appropriate to apply the same criteria for retreatment as rescue therapy.

A well baby who is not ventilated and a ventilated baby requiring no more than 40% oxygen and is stable, do not need re-treatment.

Unit price (MOH tenders):

Surfactant 6 ml : 1536 ILS

Monitoring:

Monitor for rapidly increased oxygenation and improved lung compliance. Monitor for bradycardia, cyanosis, airway obstruction, dislodgement of endotracheal tube, endotracheal tube reflux, IVH, and PVL.

Warning in administration & stability

Administration:
Intratracheal route only . Do not shake; gentle swirling/agitation is often necessary. Does not require reconstitution. Do not dilute or sonicate.

Storage: 2-8°C (36-46°F). Protect from light. Do not remove from the refrigerator for more than 24 hrs. Avoid repeated warming to room temperature. Do not return to the refrigerator more than once. For single-use only; discard any unused drug. Unopened

Vial: May refrigerate within 24 hrs if warmed to room temperature.

NOTE: (3mL) Store upright.

Thalidomide 50 mg tab

Indications:
Treatment of patients with newly - diagnosed multiple myeloma.

Level of prescriber:
Thalidomide should be prescribed by Hematologist.
The prescriber should write a report about the patient condition that necessitates its use. The report should be updated every six months.

Dose & dose adjustment:
1) 200 mg once daily at bedtime in combination with dexamethasone 40 mg po daily on days 1-4 , 9-12, and 17-20 of a 28 day treatment cycle.
   a) primary induction for transplant candidates:
   thalidomide 200 mg PO daily plus dexamethasone 40 mg PO on days 1-4 and 15-18 on even cycles and on days 1-4 on odd cycles; every 28 day.
   b) Treatment recommendations for nontransplant candidates:
   Thalidomide 200 mg PO daily (escalating to 400 mg as tolerated) or 100mg once daily for 28 day with melphalan & prednisone.
2) Treatment recommendations for maintenance therapy:
   Thalidomide 50 mg/day to start, escalated to 100 mg/day, titrated to tolerance

Duration of treatment & follow up:
No sufficient data, but study show that for induction for transplant candidates
Until remission (4- 6) months, & for maintenance for nontranspalnt patients after remission from 6 months (50 mg /daily) to 1 year (50mg every other day).

Unit price (MOH tenders):
Thalidomide 50 mg tab: (TH) 87821 ILS

Follow up:
Efficacy:
- CBC, Serum & urine M-protein by electrophoresis
- Bone marrow plasma cells

Warning & precautions:
1) If ANC ≤ 750 withhold treatment.
2) Constipation or over sedation: temporarily withhold or continue with a reduced dose.
3) Peripheral neuropathy: according to the stage either reduce the dose or discontinue.
4) Thromboembolic events: withhold therapy & initiate anticoagulant treatment, may resume treatment after resolution of thromboemolic event with maintain of anticoagulant treatment for duration of thalidomide therapy.

Pregnancy: highly teratogenic (even single dose)
- Women of childbearing age MUST be on two reliable forms of contraception
- Discontinue immediately if pregnancy occurs

Males must use latex condoms during any sexual contact with women of childbearing potential even after undergoing successful vasectomy

Administration:
- Orally with water, preferably at bed time on an empty stomach at least 1 hour after the evening meal.
- Doses ≥ 400 mg maybe given in 2-3 divided doses
- For missed dose > 12 hour wait till next dose.

Stability:
Store at 25° C, protect from light .

Trastuzumab 440mg vial

Indications:

1. Adjuvant treatment of HER2 overexpressing breast cancer.
2. Metastatic Breast Cancer as first-line or further line treatment of HER2-overexpressing metastatic breast cancer.

Level of Prescriber: oncologist.
The prescriber should write a report about the patient condition that necessitates Trastuzumab use. The report should be updated every six months.

Dose& dose adjustment:
Administer according to 1 of the following doses and schedules for a total of 52 wk of therapy.

1. Adjuvant Treatment, Breast Cancer:
   - Initial dose of 4 mg/kg IV infused over 90 min, then at 2 mg/kg weekly infused over 30 min during chemotherapy for the first 12 weeks (paclitaxel or docetaxel) or 18 week (docetaxel /carboplatin). One week following the last weekly dose of trastuzumab , administer trastuzumab at 6 mg/kg every three weeks for total one year .
   - As a single agent within three weeks following completion of multi-modality, anthracycline-based chemotherapy regimens: Initial dose at 8 mg/kg then as an Subsequent doses at 6 mg/kg every three weeks for total one year.

2. Metastatic Treatment, Breast Cancer: alone or in combination with paclitaxel, at an initial dose of 4 mg/kg infused over 90 min followed by subsequent once weekly doses of 2 mg/kg infused over 30 min disease progression Or 8 mg/kg as initial dose followed by subsequent doses of 6mg/kg every 3 weeks.

If a dose is missed for more than 1 week a loading dose should be administered as soon as possible followed by maintenance dose.

Dose adjustment: the disposition of trastuzumab is not altered based on serum creatinine.
Duration of treatment and number of cycles: schedules for a total of one year therapy (1 year study the longest one) .

Unit price (MOH tenders):
Trastuzumab 440mg vial: 14018 ILS

Warning in administration :

1. Never administer as IV push or by rapid bolus
2. Do not use DEXTROSE (5%) solution.
3. Swirl the vial gently to aid reconstitution. Do not shake.

Stability:

- stable at 2-8°C prior to reconstitution.
- vial trastuzumab reconstituted with BWFI, as supplied, is stable for 28 days after reconstitution when stored refrigerated at 2-8°C
- Diluted solution with normal saline, should be stored at 2-8°C for no more than 24 hours prior to use.

Follow up :
Efficacy: HER2 over expression is a must a 3+ve before starting treatment.
Evidence of tumor response (clinically & CA 15-3)

Warning & precautions:

1) Cardiac Monitoring for cardiomyopathy:

– Baseline LVEF measurement immediately prior to initiation of Trastuzumab.

- LVEF measurements every 3 months during and upon completion of Trastuzumab.
- Repeat LVEF measurement at 4 week intervals if Trastuzumab is withheld for significant left ventricular cardiac dysfunction
- Drug may be resumed if, within 4-8 weeks, the LVEF returns to normal & absolute decrease from baseline is 15%
- Permanently discontinue for a persistent (>8 weeks) LVEF decline or for suspension of drug on >3 occasions for cardiomyopathy

2) Pulmonary Toxicity: Pulmonary toxicity includes dyspnea, interstitial pneumonitis , pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema.
3) Hypersensitivity reaction & infusion reactions.
   - Decrease infusion rate for mild-moderate infusion reactions
   - Interrupt infusion if dyspnea or clinically significant hypotension
   - Strongly consider permanent discontinuation if severe and life-threatening infusion reactions
4) Chemotherapy-induced neutropenia may be exacerbated by trastuzumab.

Pregnancy: use when there are no alternatives and benefit outweighs risk. Monitor women using trastuzumab during pregnancy for oligohydramnios.

Lactation: discontinue nursing during trastuzumab therapy and for six months after the last dose of trastuzumab.

Zoledronic acid 4mg vial

Indications:
(Oncology):

1. Patients with multiple myeloma and patients with bone metastases from solid tumors (breast and prostate tumors) in conjunction with standard antineoplastic therapy.
2. hypercalcemia of malignancy defined as an albumin-corrected calcium of greater than or equal to 12 mg/dL

Level of prescriber: Zolendronic acid should be prescribed by Oncologists. The prescriber should write a report about the patient condition that necessitates its use . and the report must be updated every 6 months.

Dosage:

Multiple myeloma and bone metastasis from solid tumors:
4 mg as a single-dose intravenous infusion over no less than 15 minutes.

Duration of Treatment:
- Multiple myeloma and bone metastasis from solid tumors .
- every 3-4 weeks for patients with Cr. CL >60 mL/min.

Hypercalcemia of Malignancy: No more than 4 mg IV (infused over >15 minutes) once; may be repeated in 7 days. Monitor serum calcium, and wait at least 7 days before considering retreatment

Unit price (MOH tenders):
Zoledronic acid 4mg vial: 1042 ILS

Dose Adjustments:
Renal impairment (prior to initiation of therapy):

Multiple Myeloma and Bone Metastases:
Reduced Doses for Patients with Baseline CrCL< 60 ml/ min

Baseline Creatinine Clearance (mL/min)	Zometa Recommended Dose
>60	4 mg
50 – 60	3.5 mg
40 – 49	3.3 mg
30 – 39	3 mg
<30	Not Recommended

Renal impairment (Reclast)
- CrCl >35 mL/min: No adjustment needed
- CrCl <35 mL/min: Contraindicated

Renal Toxicity(during treatment):

Multiple Myeloma and Bone Metastases:
Evidence of renal deterioration : withhold dose until renal function returns to within 10% of baseline.
If albuminuria in Multiple myeloma >500 mg/24 withhold dose until return to baseline, then evaluate every 3-4 wks(reinitiate w longer infusion time at 30 min)

Hepatic impairmaint: Specific guidelines are not available.

Monitoring:

– Renal function must be carefully monitored in all pts receiving Zolendronic acid and serum creatinine must be assessed prior to each dose.

– hydration prior treatment, and electrolyte monitoring.

– Osteonecrosis of the jaw has been reported. Preventive dental exams should be performed before starting Zolendronic acid . Avoid invasive dental procedures.

– Monitor serum calcium to assess response and avoid overtreatment.

– Monitor urine every 3-4 months for albuminuria in pts with multiple myeloma.

Storage & Stability:

Store vials at 25° C. Solutions for infusion which are not used immediately after preparation should be refrigerated at 2° C to 8° C and must be completed within 24 hrs of preparation(allow to reach room Temp. prior to administration).

Dilute solutions for injection in 100 ml NS or DW prior administration. Zolendronic acid must not be mixed with calcium or other divalent cation-containing infusion solutions, such as Lactated Ringer's solution, and should be administered as a single intravenous solution in a line separate from all other drugs.