Supplementary Report

Recommendations

of NPPA regarding *anti-cancer drugs* for revision of National List of Essential Medicines-2011

National Pharmaceutical Pricing Authority
Department of Pharmaceuticals
Ministry of Chemicals & Fertilizers
Government of India

Recommendations of NPPA on inclusion of Cancer treatment Drugs in the NLEM

On the request of Department of Pharmaceuticals vide their letter No. 31026/24/2010-PI.II dated 07.08.2014, the National Pharmaceuticals Pricing Authority (NPPA) conducted a detailed study on the list of drug formulations included in the National List of Essential Medicines 2011 (NLEM 2011); and additional drugs which require inclusion in order to ensure that all lifesaving and essential drugs of mass consumption are under price control for safeguarding public interest. Based on the study, NPPA submitted its report to the department vide letter No. 23(1)/2014-Div.III/NPPA (Pt) dated 09.02.2015.

2. The recommendations of NPPA were made in two parts. The first concerning correction/ modification of anomalies/ discrepancies in description/ specification with respect to 86 drug formulations out of the 628 net formulations contained in NLEM 2011. The second concerning additional drug formulations which have been recommended for inclusion, based on the considerations of mass consumption, rationality and essentiality. The 43 medicines recommended for inclusion cover different therapeutic groups, including antipyretics, analgesics and non-steroidal anti-inflammatory; antibacterial; anti-TB; anti-malarial; anti-diabetic; cardiovascular; gastrointestinal; respiratory; and vitamins. The report did not contain recommendations relating to Cancer treatment medicines because a separate study was underway. The issue concerning inclusion of Cancer treatment medicines in the recommendations of NPPA was discussed in the meeting taken by the Secretary, Pharmaceuticals on 26.02.2015, and it was decided that the same may be submitted early so that comprehensive recommendations could go from the Department of Pharmaceuticals to the Core Committee on NLEM set up by the Ministry of Health and Family Welfare. It was clarified in the meeting that the said study has been completed and NPPA would be submitting its recommendations relating to cancer medicines immediately. Accordingly, this supplementary report containing NPPA's recommendations on revision of the list of cancer treatment medicines contained in NLEM 2011 is submitted for consideration. The recommendations conform to the

overall guidelines and direction approved by the Authority at its meeting held on 15.09.2014 and 05.02.2015

3. With respect to revision of the list of Cancer treatment medicines contained in NLEM, the NPPA consulted the Tata Memorial Centre (Mumbai) under the Department of Atomic Energy, Government of India for necessary inputs concerning incidence of the disease, and essentiality and rationality of drugs used for its treatment. At present, Cancer treatment medicines are included in Section 8 of the First Schedule to the Drugs (Prices Control) Order 2013. It covers a number of medicines under the sub-categories of Cycotoxic medicines, Hormonal and Anti-Hormonal medicines and Palliative care medicines. The Tata Memorial Centre submitted their detailed recommendations regarding addition/ deletion of drugs relating to Oncology in the NLEM. A copy of the recommendations received from them in this regard is placed at **Annexure 1**. After due examination of the recommendations received in this regard, the NPPA, with a view to obtaining comments of all stakeholders, issued a Public Notice on 21 November 2014 inviting comments Stakeholders on the recommendations made by the Tata Memorial Centre, Mumbai. A copy of the public notice issued in this regard is placed at **Annexure 2**.

4. The recommendations made by the Tata Memorial Centre, Mumbai are based on a careful review of the list of medications included in the NLEM 2011 based on the following considerations:

(i) Unequivocal proof of benefit versus previous comparator. Improvement in overall survival (OS) is ranked highest followed by disease-free and progression-free survivals (PFS) in the adjuvant and metastatic settings, respectively.

(ii) Higher priority to drugs that have the potential to cure a fraction of patients versus those that have been proven to only prolong lives in metastatic setting.

(iii) The number of patients potentially impacted in India based on data from population based cancer registries of the National Cancer Registry Programme.

(iv) The non-availability of alternative medications of the same or other pharmacological class that can act as a reasonable 'substitute'.

(v) Price of the drug to patients and the differential in price between various brands.

5. Based on the abovementioned considerations, the Tata Memorial Centre, Mumbai has recommended for deletion of three medications included at present in NLEM 2011 and addition of twelve medications that are at present not included in NLEM 2011. The gist of recommendations made by the Tata Memorial Centre for addition/ deletion are as under:-

5.1 **Drugs recommended for deletion from NLEM:**

Cytotoxic medicines:

1. **Busulphan** - restricted use mainly as a part conditioning regimen before autologous stem cell transplant.

Hormonal therapy:

1. **Raloxifene** - Restricted usage in postmenopausal women only for pharmacological prevention of breast cancer. This is rarely, if ever, practiced in India.

2. **Danazol** – Not used commonly in oncology at present.

5.2 **Drugs recommended for addition to the NLEM:**

Cytotoxic and targeted drugs:

(1) **All Trans Retinoic Acid (ATRA):**

Justification: The outcome of patients with acute promyelocytic leukemia (APL) has shown substantial improvement since the successful introduction of ATRA, the first molecularly targeted therapy in treatment of human cancer. The combination of ATRA with chemotherapy is curative in approximately 80% of patients with newly diagnosed APL.

Current cost of treatment: for 100 capsules (10 mg each) the cost is Rs 5, 795/-. The approximate total cost of treatment (for this drug) for an average sized adult is Rs. 75,000/-.

(2) **Bendamustine:**

Justification: the estimated incidence of Non-Hodgkins lymphoma (NHL) in India is 23,801 new cases per year. Bendamustine is an older drug that has been rediscovered for use in indolent (low grade) lymphomas. The most important trial with this drug has shown that the combination of Bendamustine (B) and Rituximab (R) lead to significant increase in PFS compared to nearest comparator. Moreover the B+R regimen was well tolerated with lower haematological toxicity, infections, peripheral neuropathy, and stomatitis compared to nearest comparator.

Current cost of treatment: One vial of 100 mg strength costs Rs 2, 756/-. Approximate total cost of treatment (for this drug) for an average sized adult is Rs 35, 000/-.

(3) **Rituximab:**

Justification: Rituximab is a monoclonal antibody against CD 20 antigen. For diffuse large B-cell lymphoma (DLBCL), follicular lymphoma and mantle cell lymphoma, inclusion of Rituximab in standard chemotherapy regimens has been shown to significant improve patient outcome and is standard first-line therapy for CD20-positive lymphomas.

Current cost of treatment: For innovator brand the cost of one vial of 500mg strength is Rs 25, 291/-. Approximate total cost of treatment (for this drug) for an average sized adult is Rs 2, 28, 000/-.

For the generic brands the cost of one vial of 500 mg strength is Rs 19, 695/-. Approximate total cost of treatment (for this drug) for an average sized adult is Rs 1, 32, 000/-.

(4) **Lenalidomide:**

Justification: it is an immunomodulatory and antiangiogenic drug, which is being used in wide range of cancers like multiple myeloma (in induction as well as

maintenance therapy), CLL, mantle cell lymphoma, elderly AML and MDS with 5 q del. The estimated incidence of Multiple myeloma in India is 6, 955 cases per year. There is an improved PFS and overall response (OR) in patients treated with lenalidomide plus dexamethasone versus patients treated with placebo and dexamethasone (nearest comparator). Lenalidomide reduces transfusion requirements (in 76 % of patients) and reverse cytologic and cytogenetic abnormalities in patients (36 % of cases) who have the myelodysplastic syndrome.Older patients with acute myeloid leukemia have limited treatment options and a poor prognosis. Thirty percent of elderly patients achieved CR and the median duration of CR is 10 months with the use of single agent lenalidomide. The drug is fairly well tolerated by this group of patients in whom conventional chemotherapy is contraindicated.

Current cost of treatment: the cost of 10 capsules (25 mg strength) is Rs 2, 425/-. Approximate total cost of treatment (for this drug) for an average sized adult with myeloma is Rs 60, 000/-.

(5) Trastuzumab:

Justification: Breast cancer is the most common cancer seen in Indian women with an estimated annual incidence of 1,44,937 cases. Approximately 20-25% of women with breast cancer have tumors. For women with non-metastatic breast cancer that over-expresses HER2 receptor, the addition of trastuzumab to chemotherapy reduces mortality by more than 30%. The combined hazard ratio for overall survival (OS) and disease-free survival (DFS) significantly favoured the use of trastuzumab. Even in metastatic breast cancer the addition of trastuzumab to standard chemotherapy is associated with increased overall survival as seen in multiple trials.

Current cost of treatment: the cost of one vial of- 440 mg strength is Rs 50,583/-. Approximate total cost of treatment (for this drug) for an average sized adult is Rs 800,000/-.

For the generic brands the cost of one vial of 440 mg strength is Rs 45, 000/-. Approximate total cost of treatment (for this drug) for an average sized adult is Rs 6, 75, 000/-.

(6) **Capecitabine**

Justification: It is used in the adjuvant setting in many gastrointestinal cancers, including stomach and colorectal. The estimated annual incidence of GI cancer in India is 1,99,926. Capecitabine is also used in other cancers like advanced breast, pancreatic, esophageal, etc. where its use is associated with prolongation in progression-free survival and good symptomatic palliation to patients.

Current cost of treatment: The cost of innovator brand for 10 tablets (500 mg strength each) is Rs 577. Approximate total cost of treatment (for this drug) for an average sized adult is Rs 30, 000/-.

The cost of generic brand for 10 tablets (500 mg strength each) is Rs 277. Approximate total cost of treatment (for this drug) for an average sized adult is Rs 14, 000/-.

(7) **Temozolomide (TMZ):**

Justification: This is a novel alkylating agent used in management of malignant gliomas. Positive therapeutic evidence for improvement in overall survival rates in glioblastoma The estimated annual incidence of Brain tumor in India is 18, 831. It is also used in the palliative treatment of resistant neuroendocrine tumors and malignant melanoma.

Current cost of treatment: The cost of innovator brand for 5 capsules (250 mg strength each) is Rs 24, 000/-. Approximate total cost of treatment (for this drug) for an average sized adult is Rs 2, 16, 000/-.

The cost of generic brand for 5 capsules (250 mg strength each) is Rs 1, 826/-. Approximate total cost of treatment (for this drug) for an average sized adult is Rs 20, 000/-.

(8) **Irinotecan:**

Justification: This is a camptothecin derivative, used in various cancers such as colorectal, gliomas, glioblastomas, esophageal, stomach, cervical, ovarian, lung and mesothelioma. This drug is mainly used in recurrent and second line setting in many of these cancers where its use leads to PFS benefit and useful symptomatic palliation.

Current cost of treatment: The cost of innovator brand for one vial of 100 mg strength is Rs 7, 780/-. Approximate total cost of treatment (for this drug) for an average sized adult is Rs 1, 87, 000/-.

The cost of generic brand for one vial of 100 mg strength is Rs 918/-. Approximate total cost of treatment (for this drug) for an average sized adult is Rs 25, 000/-.

(9) **Erlotinib:**

Justification: Lung cancer is the leading cause of death among Indian men and women. The estimated annual incidence of lung cancer in India is 70, 275. Use of Erlotinib either in first- or second line setting is associated with a response rate of rate of 71. When Erlotinib is used upfront in patients with EGFR mutation positive, it is significantly superior to chemotherapy in terms of PFS and response rate. Moreover Erlotinib proved to be better tolerated than chemotherapy.

Current cost of treatment: The cost of innovator brand for 10 tablets (150 mg strength each) is Rs 16, 358/-. Approximate total cost of treatment (for this drug) for an average sized adult is Rs 3, 00, 000/-.

The cost of generic brand for 30 tablets (150 mg strength each) is Rs 2, 730/-. Approximate total cost of treatment (for this drug) for an average sized adult is Rs. 18, 000/-.

Palliative and supportive medicines:

(10) Zoledronic acid:

Justification: This drug of the bisphosphonate class is an osteoclast inhibitor that that has been found to reduce the incidence of skeletal related events (severe pain, fracture, etc.) in patients with multiple myeloma and a variety of solid tumors (breast, lung, kidney, prostate, etc.) that are metastatic to the bone. It has also shown better result in terms of OS and PFS compared to clodronic acid.

Current cost of treatment: The cost of innovator brand for one vial of 4 mg strength is Rs 10,000. Approximate total cost of treatment (for this drug) for an average sized adult is Rs 120,000.

The cost of generic brand for one vial of 100 mg strength is Rs 265/-. Approximate total cost of treatment (for this drug) for an average sized adult is Rs 3, 180/-.

Hormonal therapy:

(11) Megestrol acetate:

Justification: This is a progestogenic drug that is used in metastatic hormone receptor positive breast cancer, endometrial stromal sarcoma and endometrial cancer. The estimated number of hormone receptor positive metastatic breast cancer in India is 72, 468. Megestrol use in metastatic breast cancer is associated with response rate (CR, PR, or stable disease) of 65%. Toxicity was minimal, and side effects consisted primarily of weight gain, which was seen in 14.5% cases. Megestrol acetate can provide effective palliation in patients with advanced breast cancer.

Current cost of treatment: The cost of 10 tablets (40 mg strength each) is Rs 189. Approximate total cost of treatment (for this drug) for an average sized adult assuming 6 months of treatment is Rs 12, 000/-.

(12) **Letrozole:**

Justification: This drug belongs to a class of drugs that reduce estrogen to very low levels in postmenopausal women due to inhibition of the enzyme aromatase. The principal use of this drug is as an adjuvant therapy in postmenopausal women with estrogen receptor (ER) positive breast cancer where it has been shown to result in PFS and OS benefit compared to tamoxifen. The estimated annual incidence of ER positive non-metastatic breast cancer in postmenopausal women in India is 25, 000. In the early Breast Cancer Trialists Collaborative Group metaanalysis the use of aromatase inhibitors (versus tamoxifen) has been shown to reduce the risk of recurrence by 38%, risk of death by 30% and risk of contralateral breast cancer by 40%. Letrozole is also used in treatment of metastatic endometrial cancer and endometrial stromal sarcoma.

Current cost of treatment: The cost of innovator brand for 10 tablets (2.5 mg strength each) is Rs 1, 568/-. Approximate total cost of treatment (for this drug) for an average sized adult is Rs 2, 82, 000/-. The cost of generic brand for 10 tablets (2.5 mg strength each) is Rs 46. Approximate total cost of treatment (for this drug) for an average sized adult is Rs 8, 280/-.

6. In response to the public notice dated 24 November 2014 issued by NPPA, six representations were received from the industry. The representations are placed at Annexure 3, 4, 5, 6, 7 and 8, respectively. The gist of comments received are tabulated below:-

Sl. No.	Association / Company's Name	Comments
1.	Organization of Pharmaceutical Producer of India (OPPI) - NPPA-2014/190 dated:	Tata Memorial Centre (TMC)'s recommendations run contrary to the objective of NLEM i.e. to list out minimum number of medicines that would cater to the maximum health care burden in the most cost effective manner. TMC has listed out drugs for the reasons like price variations and

Sl. No.	Association / Company's Name	Comments
	12.12.2014	analysis of therapeutic substitutes and the basic question of essentiality has not been addressed due to absence of nationwide epidemiological data in respect of diseases mentioned in their recommendations. OPPI has also stated that the drugs mentioned in the TMC recommendations may be used by the hospitals in treating its patients but do not qualify to be a part of NLEM as they do not necessarily cater to majority healthcare needs of the country and excessive price control would discourage innovators from bringing new targets therapies in the market. In this regard, OPPI has furnished comments about certain Cancer treatment drugs namely Trastuzumab, Erlotinib, Rituximab, Letrozole, Zoledronic Acid and Irinotecan in their representation.
2.	M/s Roche - letter dated 05.12.2014	TMC's recommendations into NLEM are based on drug demonstrating significant impact in terms of improving clinical outcomes. However, the prevalence / burden of the diseases, for which proposed drugs are prescribed, is not very high and therefore may not classify as a priority healthcare need of nation in accordance with the objective of NLEM. The company has also stated that TMC recommended drugs are not used for so common indications and affect a very limited Indian population being treated only at tertiary level and neither included in the Indian Pharmacopoiea nor in the National formulary of India. They have objected to proposed inclusion of Trastuzumab, Erlotinib and Rituximab in the NLEM.

Sl. No.	Association / Company's Name	Comments
3.	M/s Biocon – RA/BL/NPPA/14/001 dated 08.12.2014	The company has submitted comments in respect of only one Cancer treatment drug 'Trastuzumab' launched by them in 2014, stating that it is the world's most affordable drugs used for treatment of a highly prevalent form of breast cancer. The company has stated that it is important to provide adequate incentive to the Bio Pharmaceutical Industry to continue to bring products like 'Trastuzumab' in the market and therefore to avoid inclusion of the same under price control.
4.	M/s Mylan – letter dated 09.12.2014	The company has submitted comments on the oncology drugs 'Trastuzumab' in specific, and has stated that the bio-similar 'Trastuzumab' was launched by them at significantly reduce price i.e. 25% less than the innovator price and they are confident that would be able to further reduce the cost of manufacturer of 'Trastuzumab'. The company has also mentioned that 4 brands of 'Trastuzumab' are available in Indian market and requested for not including oncology drugs in general and 'Trastuzumab' in specific under price control.
5.	M/s MSD - letter dated 11.12.2014	The company has stated that the drug 'Temozolomide' is covered under TMC recommendation and the price of their brand is not correctly provided by the TMC. They sought extension of time for submission of their comments upto 22.12.2014 but the same has not been received.
6.	M/s Panacea Biotec – letter dated 01.01.2015	The company has made submissions in respect of two drugs, namely, 'Rituximab' & 'Trastuzumab', recommended by the TMC for inclusion into the NLEM and has suggested

Sl. No.	Association / Company's Name	Comments
		that keeping these category of drugs (i.e. monoclonal antibody) under price control is not a solution, as it would be little premature to decide controlling prices of biologics / bio-similar products. Such products should be left to the market forces for now and allow more bio-generic players to enter this area. The company has specifically mentioned to allow patient access to the products directly from the manufacturers at price to stockists.

7. After careful examination of the recommendations received from the Tata Memorial Centre, Mumbai; the comments received from the industry; and the MAT value, volume and price data with respect to these medications, which is placed at **Annexure 9**, the NPPA makes the following recommendations for inclusion/ delction of drug formulations related to cancer treatment in the NLEM:-

7.1 **The Tata Memorial Cent, Mumbai has recommended for deletion of Busulphan, Raloxifiene and Danazol from the NLEM.** The ceiling price of Busulphan tablet 2 mg has been fixed at Rs. 3.41 per tablet vide S.O. No. 3363 (E) dated 05.11.2013, which has been revised as per WPI to Rs. 3.63/ tablet vide S.O. No. 1156(E) dated 28.04.2014. The ceiling price of Raloxifene tablet 60 mg has been fixed at Rs. 9.89 per tablet vide S.O. No. 1616 (E) dated 14.06.2013, which has been revised as per WPI to Rs. 10.52/ tablet vide S.O. No. 1156(E) dated 28.04.2014. The ceiling price of Danazol capsule 50 mg has been fixed at Rs. 9.37 per tablet vide S.O. No. 1607 (E) dated 14.06.2013, which has been revised as per WPI to Rs. 9.96/ tablet vide S.O. No. 1156(E) dated 28.04.2014. The volume of sales of Busulphan, Raloxifene and Danazol in the retail market appears to be negligible, and hence, given the scientific reasons put forth by the Tata Memorial Centre, **NPPA endorses the recommendation of the Tata Memorial Centre, Mumbai to delete these three medicines from the NLEM.**

7.2 **With respect to the 12 drugs recommended by the Tata Memorial Centre, Mumbai for inclusion,** the views of NPPA are as under:-

(i) **ATRA (All Trans Retinoic Acid):** No representation against its proposed inclusion has been received from manufacturers. The total requirement would be for around 5,000 new cases per year in India. **NPPA endorses the recommendation of the Tata Memorial Centre, Mumbai for inclusion of ATRA in the NLEM.**

(ii) **Bendamustine:** This is an old molecule and better molecules are available. Moreover, the MAT volume and value for this drug formulation are also quite low. Hence, **NPPA does not recommend inclusion of this drug in the NLEM.**

(iii) **Rituximab:** We have received representations against this from the industry. However, in the representation of OPPI, it accepts that the drug may be required by approximately 25,000 new cases every year in India. Apart from the innovator brand (MABTHERA from Roche), generic brands are available from several Indian manufacturers. The MAT value (all strengths and dosage forms) is around Rs. 90 crore in the retail market. **NPPA endorses the recommendation of the Tata Memorial Centre, Mumbai for inclusion of Rituximab in the NLEM.**

(iv) **Lenalidomide:** Very few representations have been received against inclusion of this drug in the NLEM. The MAT value (all strengths and dosage forms) is around Rs. 8 crore in the retail market. **NPPA endorses the recommendation of the Tata Memorial Centre, Mumbai for inclusion of Lenalidomide in the NLEM.**

(v) **Trastuzumab:** Some representations are against the inclusion of this particular drug in the NLEM. However, this drug is required by a large number of patients every year and it has been recommended even in WHO Model list of Essential medicine. The MAT value (all strengths and dosage forms) is around Rs. 92 crore in the retail market. **NPPA endorses the recommendation of the Tata Memorial Centre, Mumbai for inclusion of Trastuzumab in the NLEM.**

(vi) **Capecitabine:** This is a first line drug for cancer. No representations have been received against the inclusion this drug, which is available from many generic versions. The MAT value is around Rs. 27 crore (all strengths and dosage forms). Given the high incidence of the disease

in the country, **NPPA endorses the recommendation of the Tata Memorial Centre, Mumbai for inclusion of Capecitabine in the NLEM.**

(vii) **Temozolomide:** No representation has been received against this drug's inclusion in the NLEM except from MSD on pricing issue. The MAT value (all strengths and dosage forms) is around Rs. 38 crore. Given the high incidence of the disease, **NPPA endorses the recommendation of the Tata Memorial Centre, Mumbai for inclusion of Temozolomide in the NLEM.**

(viii) **Irinotecan:** Representation against inclusion of this drug in the NLEM have been received. The Tata Memorial Centre itself admits that this is not a first line drug. Hence, **NPPA does not recommend the inclusion of Irinotecan in the NLEM.**

(ix) **Erlotinib:** OPPI has argued that since it is patents drug, it should not be brought under price control. But it is seen that there are a number of generic versions of Erlotinib available in the market. Given the high incidence of the disease, this drug is a good candidate for inclusion in the NELM. The MAT value of Erlotinib (all strengths and dosage forms) is around Rs. 25 crore. **NPPA endorses the recommendation of the Tata Memorial Centre, Mumbai for inclusion of Erlotinib in the NLEM.**

(x) **Zoledronic acid:** This is required in bone metastasis. The contention of OPPI that "Denosumab is a superior drug compared to zoledronic acid" does not mean that zoledronic acid cannot be included in NELM. **NPPA endorses the recommendation of the Tata Memorial Centre, Mumbai for inclusion of Zoledronic acid in the NLEM.**

(xi) **Megestrol acetate:** It is a supplemental therapy in many treatment regimens. No representations have been received against its inclusion in the NLEM. **NPPA endorses the recommendation of the Tata Memorial Centre, Mumbai for inclusion of Megestrol acetate in the NLEM.**

(xii) **Letrozole:** Only one representation against inclusion of this drug. The annual incidence of this drug is over 25,000. The MAT value is estimated around Rs. 13 crore (all strengths and dosage forms). **NPPA endorses the recommendation of the Tata Memorial Centre, Mumbai for inclusion of Letrozole in the NLEM.**

8. **Conclusion**: Accordingly, NPPA recommends the deletion of Busulphan, Raloxifene and Danazol from the First Schedule to the DPCO 2013/ NLEM 2011, and inclusion of all strengths and dosage forms of ATRA (All Trans Retinoic Acid), Rituximab, Lenalidomide, Trastuzumab, Capecitabine, Temozolomide, Erlotinib, Zoledronic acid, Megestrol acetate and . Letrozole. The combined MAT value of the 10 additional drugs recommended for inclusion in the NLEM/ First Schedule to the DPCO 2013 is estimated to be around Rs. 300 crore.

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