



Drug Information Bulletin

Drug Information Centre (DIC)

Indian Pharmaceutical Association

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Content

- *Editorial*
- *New Drug: Nusinersen for spinal muscular atrophy*
- *Azithromycin Risk of haematological relapses*
- *Atorvastatin and antivirals: interaction Increase in atorvastatin plasma levels*
- *Fluoroquinolone antibiotic: Risk of tendon damage and neuropathies*
- *Glimps of Refreshers course for Practicing Pharmacists by IPA, Bengal Branch*
- *Forthcoming Event*

Editorial

Good news for millions of cancer patients as MRP of 42 anticancer drugs and 390 formulations has been fixed by the National Pharmaceutical Pricing Authority (NPPA) under the ministry of Chemicals and Fertilizers with effect from 8th March 2019. It is reported that through this move prices reduced by up to 87 percent. According to the government, the price cut is expected to benefit about 22 lakh cancer patients in India and would result in annual savings of around ₹800 crore to the patients.

It is obviously a good move but shifting the price monitoring policy from DPCO 2013 to self monitoring mechanism developed apprehension among the experts. They thought that this policy will weaken the National Pharmaceutical Pricing Authority in monitoring price of medicines.



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New Drug: Nusinersen for spinal muscular atrophy

Approved indication: spinal muscular atrophy
Spinraza (Biogen)

single-dose vials containing 12 mg/5 mL solution for injection

Nusinersen is an orphan drug approved for the treatment of 5q spinal muscular atrophy. This is a rare genetic disease (approximately 1 in 10,000 births) which presents as progressive muscle weakness and atrophy. Until now, there have been no treatments for this disease.

Spinal muscular atrophy is classified into four types depending on age of onset and motor function:

- type 1 – onset 0–6 months, life expectancy less than 2 years
- type 2 – onset 6–18 months, life expectancy 10–40 years
- type 3 – onset after 18 months, life expectancy adulthood
- type 4 – onset after 5 years, life expectancy adulthood.

Approximately half of patients that present are babies with type 1 disease.

Patients with spinal muscular atrophy have insufficient levels of the survival motor neuron (SMN) protein which is essential for the survival and functioning of motor neurons. This protein is encoded by two genes – SMN1 and SMN2. In spinal muscular atrophy the SMN1 gene is lacking but SMN2 is present so patients produce a truncated form of the protein. Having fewer copies of the SMN2 gene is generally associated with earlier onset of disease and more severe symptoms. Nusinersen is a synthetic antisense oligonucleotide which works by enabling the SMN2 gene to produce a full length SMN protein.

Nusinersen 12 mg is administered by lumbar puncture. It should be given at 0, 2, 4 and 9 weeks followed by a maintenance dose every four months. The drug's terminal half-life in the cerebrospinal fluid is 19–25 weeks and it is mainly excreted in the urine. Nusinersen is metabolised by exonucleases, and drug interactions with the cytochrome P450 system have not been found.

The approval of nusinersen is based on several trials in patients aged from 30 days to 15 years. In

babies, motor milestones were measured using scales such as the Hammersmith Infant Neurological Examination (HINE) which included evaluation of kicking, head control, rolling, sitting, crawling, standing and walking. The Hammersmith Functional Motor Scale-Expanded (HFMSE) score was used to assess older children. This scale ranges from 1 to 66 with higher scores indicating better motor function.

A phase III randomised, placebo-controlled trial (ENDEAR) included 121 babies aged seven months or younger with type 1 disease. At baseline, all of them were hypotonic and most had delayed motor function development and limb weakness. After six injections of nusinersen or a placebo (0, 2, 4, 9 weeks then 6 and 10 months), half of those given nusinersen (37/73) had achieved motor milestones compared with none (0/37) of those given a sham injection. In the nusinersen group, 22% of babies developed full head control, 10% could roll over, 8% could sit unaided and 1% were able to stand. At the final analysis, 16% of the babies treated with nusinersen had died compared with 39% treated with a sham injection. A lower proportion of babies who received nusinersen had died or required permanent ventilation compared with those in the control group (39% vs 68%).¹ Improvements in motor milestones were also observed in an uncontrolled phase II trial (20 babies) with open-label 6–12 mg and 12 mg doses of nusinersen.²

A second randomised, controlled phase III trial (CHERISH) enrolled 126 children with later-onset disease whose symptoms started after six months of age (type 2 and 3 disease). At baseline, they had a median age of 3–4 years. All of them were able to sit, some could walk with support, but none could walk independently. After 15 months (treatment given at 0, 1, 3 and 10 months), children in the nusinersen group (n=84) had improved by 4 points on the HFMSE scale whereas those in the sham-injection group (n=42) had got worse by 1.9 points. (A change of at least 3 points on this 66-point scale is considered to be clinically meaningful.) The proportion of children who were able to stand independently at 15

months was no different with nusinersen than with the sham injection (1/84 vs 1/42).³

Adverse events were similar between the treatment and the control arms. The most common events with nusinersen were fever, constipation, rash, respiratory tract infection, pneumonia, nasopharyngitis and bronchiolitis. Reactions associated with lumbar puncture, like headache, back pain, vomiting and post-lumbar puncture syndrome, were also reported.

Thrombocytopenia, coagulation abnormalities and renal toxicity have occurred with other antisense oligonucleotides. Decreased platelet counts and elevated urine protein have been observed in some patients treated with nusinersen so blood and urine testing may be needed before or during treatment.

Nusinersen is the first treatment to be approved for spinal muscular atrophy in Australia. It seems to improve motor function in babies and children, but it is not yet known if the benefits will be sustained in the longer term and increase survival. Patients who completed the ENDEAR and CHERISH trials have been enrolled in an extension study (SHINE trial) which is planned to continue until 2023 and results have not yet been reported.

References

1. Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. *N Eng J Med* 2017;377:1723-32.
2. Finkel RS, Chiriboga CA, Vajsar J, Day JW, Montes J, De Vivo DC, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. *Lancet* 2016; 388:3017-26.
3. Mercuri E, Darras BT, Chiriboga CA, Day JW, Campbell C, Connolly AM, et al. Nusinersen versus sham control in later-onset spinal muscular atrophy. *N Engl J Med* 2018;378:625-35.

Ref. Australian Prescriber

Note: As far as information available this is the only drug for treatment of SMA, but not yet approved by CDSCO and cost is prohibitive.

Azithromycin Risk of haematological relapses

The HSA has announced that a clinical trial, investigating effectiveness of long-term azithromycin to prevent bronchiolitis obliterans syndrome (BOS) in certain haematological patients, was terminated prematurely because of an increase in the rate of haematological malignancy relapses and mortality in patients that had a haematopoietic stem cell transplantation (HSCT). Azithromycin is a macrolide antibiotic. It is not approved for the prophylaxis of BOS in HSCT patients. There are 15 generic azithromycin-containing products registered in Singapore. The aim of the clinical trial was to investigate if early administration of azithromycin could improve airflow decline-free survival two years after allogeneic HSCT. The trial investigators concluded that early administration of azithromycin for prophylaxis of BOS in HSCT patients resulted in worse airflow decline-free-survival than did placebo. However, the findings were limited by the early termination of the trial and further investigation was required.

Reference: Product Safety Alerts, HSA, 28 December 2018 (<http://www.hsa.gov.sg/>) (See WHO Pharmaceuticals Newsletter No.6, 2018: Increased risk of cancer relapse in donor stem cell transplant patients in USA)

Atorvastatin and antivirals: interaction Increase in atorvastatin plasma levels

The Egyptian Pharmaceutical Vigilance Center (EPVC) has announced that the product information for atorvastatin will be updated to include a warning about the potential increase in atorvastatin levels when coadministered with elbasvir/grazoprevir and glecaprevir/pibrentasvir. The combined use of glecaprevir/pibrentasvir with atorvastatin is now contraindicated. Atorvastatin is a synthetic lipid-lowering agent indicated for the prevention of cardiovascular diseases and hypercholesterolaemia. Elbasvir/grazoprevir and glecaprevir/pibrentasvir preparations are indicated for the treatment of hepatitis C (HCV). Risk of myopathy may be increased with the concomitant use of atorvastatin and antivirals for treatment of HCV. Reference: Newsletter, EPVC, December 2018 (www.epvc.gov.eg) Axitinib Risk of interstitial lung disease Japan. The MHLW and the PMDA

have announced that the package insert for axitinib (Inlyta®) should be revised to include interstitial lung disease as an adverse drug reaction. Axitinib is indicated for the treatment of unresectable metastatic renal cell carcinoma. A total of 20 cases involving interstitial lung disease have been reported in patients treated with axitinib in Japan during the previous three fiscal years. A causal relationship with the product could not be excluded in two of these cases. MHLW/PMDA concluded that the revision of the package insert was necessary based on the results of the investigation of the currently available evidence.

Reference: Revision of Precautions, MHLW/PMDA, 10 January 2019 (www.pmda.go.jp/english/)

Fluoroquinolone antibiotic: Risk of tendon damage and neuropathies

The Health Products Regulatory Authority (HPRA) has updated the Summary of Product Characteristics (SmPC) and Package Leaflets (PL) for all fluoroquinolone antibiotics to include tendonitis, tendon rupture, neuropsychiatric effects and neuropathies associated with paraesthesia as adverse reactions. The update followed conclusions from a recent review by EMA's Pharmacovigilance Risk Assessment Committee (PRAC)'s. Fluoroquinolones are a class of broad spectrum antibiotics and include ciprofloxacin, levofloxacin, ofloxacin and moxifloxacin. The PRAC recommended that fluoroquinolone antibiotic use should be further restricted, and the information provided to patients on potential adverse reactions should be expanded to emphasize the possibility of persisting effects.

Reference: Drug Safety Newsletter, HPRA, December 2018 (www.hpra.ie)

Glimps of Refreshers course for Practicing Pharmacists by IPA, Bengal Branch



Forthcoming Event:

June 12-14 2019

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19th International Congress of the International Society for Ethnopharmacology



Ethnopharmacology - Bridging cultures and continents

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