CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

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The Methotrexate Shortage

To the Childhood Cancer Community:

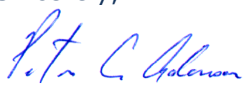
I wanted to update the community on the status of the methotrexate drug shortage. Over the past few weeks, the supply of *preservative free* methotrexate (PF-MTX) reached critically low levels in the United States. This shortage may impact the care of children with acute lymphoblastic leukemia, certain lymphomas, osteosarcoma and select other childhood tumors. (The attached page contains a brief summary on PF-MTX and why it is such a critical part of treatment for our children.)

Officials at the FDA continue to work hard to secure the methotrexate supply needed, and based on reports earlier today, a near term solution to the shortage is emerging. This indeed is very encouraging news. However, until we are confident that every center that cares for children with cancer who require treatment with methotrexate has drug available at their center, members of the Children's Oncology Group will not consider the crisis fully resolved. Based on information provided by the FDA, we hope that this goal can be achieved in the upcoming days, and certainly to no longer than one to two weeks.

It is taking the combined effort of our entire community to help us assure that the best treatments remain available, without interruption, for children with cancer throughout the United States. Numerous medical organizations, advocacy groups, parents, friends, the FDA, the National Cancer Institute, industry leaders and members of Congress and Senate worked together, and continue to work together, to find solutions that work. The remarkable way our community has responded to this unprecedented crisis, I believe, speaks volumes about who we are.

Although our efforts to fully resolve the crisis must continue, on behalf of the Children's Oncology Group's physicians, nurses, pharmacists, psychologists, laboratory scientists and other allied health professionals, I thank everyone for their support and commitment. The children and their families that members of the COG helps care for always continue to inspire us. Thank you.

Sincerely,



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Methotrexate

Methotrexate was a drug discovered in the 1950s. Since the 1960s, administration of methotrexate by mouth has been a cornerstone of maintenance chemotherapy for children with the most common childhood cancer, acute lymphoblastic leukemia (ALL). It was during the 1960s that we learned that injecting methotrexate into the spinal fluid (intrathecal administration) was critically important in helping to prevent the spread of leukemia to the covering of the brain and spinal cord. Thus for more than 40 years, all children with acute lymphoblastic leukemia receive intrathecal MTX as a part of their cancer treatment.

In addition to ALL, administering methotrexate in very high doses has proven important for the treatment of a number of other cancers, including certain leukemias, lymphomas and bone cancer (osteosarcoma).

There are essentially three forms of methotrexate currently used to treat children with cancer: oral methotrexate, intravenous methotrexate, and *preservative free* methotrexate. The current shortage only affects preservative free methotrexate, not oral or low dose intravenous MTX.

Concerns on Utilizing Preservative Containing Methotrexate

Intravenous concerns:

Similar to a number of intravenous solutions, methotrexate for injection contains the preservative benzyl alcohol. In the late 1970s/early 1980s, research found that benzyl alcohol administration could produce significant, life threatening side effects in pre-term infants. This apparently resulted from the inability of pre-term infants to efficiently metabolize (remove from the body) benzyl alcohol. Older infants, children and adolescents generally do not experience any side effects when exposed to standard amounts of this preservative.

There are a few reports, however, of older children who developed apparent benzyl alcohol side effects when exposed to very high intravenous doses of the preservative, such as which may occur with high dose methotrexate administration. The product label approved by the FDA has a warning that states that preservative containing MTX solutions should not be administered when prescribing high dose MTX.

Intrathecal (into the spinal fluid) concerns:

In the late 1970s/early 1980s, reports also emerged about the potential severe side effects of benzyl alcohol when given into the spinal fluid, including reports of paralysis. Although this risk may be rare, avoiding benzyl alcohol by using *preservative free* MTX has been the standard of care for many years. Thus the MTX product label also contains a warning not to administer preservative (benzyl alcohol) containing drugs into the spinal fluid.

About the Children's Oncology Group

The Children's Oncology Group (childrensoncologygroup.org), a National Cancer Institute supported clinical trials group, is the world's largest organization devoted exclusively to childhood and adolescent cancer research. The Children's Oncology Group (COG) unites more than 7,500 experts in childhood cancer at more than 200 leading children's hospitals, universities, and cancer centers across North America, Australia, New Zealand, and Europe in the fight against childhood cancer. COG research has turned children's cancer from a virtually incurable disease 50 years ago into one with an overall cure rate approaching 80 percent today. Research conducted by the COG is also supported through the generosity of individuals, corporations and private foundations working with The Children's Oncology Group Foundation (TheCOGFoundation.org), which enables philanthropic resources to go directly to COG's worldwide team of researchers committed to turning new discoveries into better treatments.