CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

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The Methotrexate Shortage

To parents and families of children cared for at COG institutions:

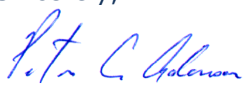
Over the past week, there has been increasing news coverage about the methotrexate drug shortage in the United States. I am writing to share news that real solutions to this shortage appear to have emerged, such that any child with cancer who requires treatment with methotrexate should indeed be able to receive the drug. Additional information on this specific drug shortage is contained on the attached page.

More specifically, based on reports received this morning from the Food & Drug Administration (FDA), an emergency supply of methotrexate is now available, with planned releases of additional drug from other pharmaceutical companies expected in the upcoming days and weeks. We will continue to monitor this situation closely. Institutions requiring methotrexate for their patients that need assistance on how best to obtain drug can access additional information through the Children's Oncology Group or the FDA's Office of Drug Shortages.

We recognize that these events have created understandable anxiety, and are grateful that the childhood cancer community advocated so well in efforts to address the drug shortage. It is important to note that brief delays in cancer drug administration, which may occur for a variety of reasons, are not uncommon during the course of cancer treatment. We are thus reassured that as drug is again available, children should not have to experience a significant delay or change in their treatment due to the shortage. Your physician will be the best person to address any additional specific concerns you may have about your child's care.

As a research organization committed to improving the outcome for all children with cancer, the Children's Oncology Group remains indebted to children and families that participate in research. The methotrexate shortage, however, was one that we believed required our active participation in the advocacy necessary to fully address an unacceptable situation.

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.