How can we ensure child-friendly oral chemotherapy agents are available?

In this article, Jane Buckham, reviews the availability of unlicensed oral cytotoxic formulations that are “paediatric friendly” in the UK and assesses their marketing potential. Where licensing is unlikely to be feasible the risks involved in using unlicensed preparations are discussed.

Historically hospital pharmacy departments compounded suitable paediatric medicines from adult solid dose preparations or injections in order to improve compliance and provide accurate dosing. This is particularly important with chemotherapy because of the narrow therapeutic margin between treatment and toxicity. Such extemporaneous manufacturing was unregulated and consequently product integrity unassured.

The Medicines and Healthcare products Regulatory Agency allows small scale manufacture of unlicensed formulations in manufacturing sites that have a UK “specials” licence. Manufacturers must comply with Good Manufacturing Practice standards for both production and quality control. Such production, according to the European directive 2001/84/EC, is “to meet the special needs of an individual patient”. Manufacturers are, therefore, not allowed to inform other clinicians or pharmacists that they have developed a suitable product. This results in multiple formulations for some medicines in circulation, with different strengths and different excipients. What a child receives from a hospital pharmacy may not be bioequivalent to a preparation received from a community pharmacy or another hospital. It may also have different physical, chemical and microbial stability. Of particular concern is the drug concentration, which can result in errors in administration. This “specials” licensing arrangement is currently under review by the MHRA, which is aware of the large number of formulations available.

Licensed medicines are only granted a marketing authorisation once safety, efficacy and quality have been demonstrated. In prescribing unlicensed medicines, the prescriber, rather than the manufacturer, is at risk of litigation in the event of adverse events. There is some evidence that fewer adverse reactions occur in children treated with licensed medicines than unlicensed ones. Exclusivity incentives for paediatric medicines development that have been in place for a number of years, such as the Best Pharmaceuticals for Children Act in the US, have led to an improvement in licensing of selected medicines, particularly for older children. However such legislation may not be sufficient to ensure all new drugs with potential use in children are licensed.

In six years of licensing (1995–2001) the European Medicines Agency (EMA) only approved 17 paediatric licences (24 per cent) of 120 applications for medicines that could be of potential benefit to children. Of these only temozolamide from age three years and rituximab for all ages were licensed for paediatric oncology. The EMA has posted a consultation document outlining the medicines which it would like to license, where information about safe use is inadequate for children. The consultation document EMEA/384641/2006, “Assessment of the paediatric needs — chemotherapy products (part 1)”, relates to paediatric oncology products. Although it is
Panel 1: Oral cytotoxics

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Advantages/disadvantages</th>
<th>Availability of “specials”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablet</td>
<td>Compact, smaller dose increments than licensed strength. Expensive and requires large batch production. Need to be swallowed. Halving and quartering adult tablets is inaccurate.</td>
<td>Cyclophosphamide 25mg Mercaptopurine 10mg</td>
</tr>
<tr>
<td>Capsule</td>
<td>Small batches by hand in small dose increments, less accurate drug distribution than large scale milling and batch production. Need to be swallowed.</td>
<td>Busulfan 25mg Thioguanin 10mg</td>
</tr>
<tr>
<td>Melts</td>
<td>Easy for small children to take. More stability issues with drug/exipient combinations. Cytotoxics need to be washed down after taking with a drink.</td>
<td>None at present</td>
</tr>
<tr>
<td>Micropellets</td>
<td>Easy for small children to take. Cytotoxics need to be washed down after taking with a drink. Accuracy in dosing may be difficult in ensuring even drug distribution and release from pellets.</td>
<td>None at present</td>
</tr>
<tr>
<td>Liquids</td>
<td>Easy to take. Instability of cytotoxics in solution can be a problem. Spillage. Need to be washed down with a drink.</td>
<td>Busulfan, cyclophosphamide, mercaptopurine, methotrexate, procarbazine, temozolamide, thioguanine</td>
</tr>
<tr>
<td>Injection taken orally</td>
<td>May not be same parent compound as oral preparations. No flavourings to improve palatability.</td>
<td>Etoposide</td>
</tr>
<tr>
<td>Powders</td>
<td>Need to be made to individual doses. Impractical for batch production. High risk of contamination.</td>
<td>Imatinib</td>
</tr>
</tbody>
</table>

The list of available products (Panel 2) and current “specials” production units listed in the BNF 2008 were compiled by the Neonatal and Paediatric Pharmacists Group in the UK and were reviewed by formulation type then by current product availability in August 2008.

All “specials” production units listed in the BNF 2008 were contacted for details of products and shelf life. E-mail requests for information were followed up by telephone until all units were contacted.

Marketing potential of existing “specials” was assessed by potential demand for a formulation and its shelf life. Shelf life was considered to be a minimum of one year from manufacture for viability. Shelf life could be extended for some products by reformulation but this would require a major investment of resources.

Demand in the UK was estimated from the number of patients with a tumour type and staging that would benefit from the “special”. Information was provided from the 2006 Childhood Cancer and Leukaemia Group registry. The same information was processed for 2005 and 2007 to ensure that this was a typical year. Suspensions were considered appropriate for children aged under nine years. Annual use was obtained from treatment guidelines and clinical trials for doses, and proportion of children requiring relevant courses, according to their staging. This takes no account of use for non-malignant conditions or in adult patients with swallowing difficulties.

Formulations

Panel 1 outlines the advantages of different formulations that could be produced, with examples of cytotoxic “specials” that are currently available.

In the UK there are 24 NHS production facilities and 10 commercial units licensed to produce “specials”. Owing to the containment and health and safety issues, of these only six NHS units and two commercial units have the facilities to produce cytotoxics.

The NHS manufacturing units maintain a database (Pro-file) of products produced by their members but, because of the prohibition on advertising “specials” by the MHLRA, this list is only available to NHS purchasers, and information is not available from commercial “specials” manufacturers. The list is voluntary so is often incomplete. Formulations included on Pro-file are marked * in Panel 2.

The list of available products (Panel 2) and manufacturers includes both “specials” and clinical trial supplies and was compiled by contacting each supplier (since the Pro-file database is thought to be incomplete). The list comprehensively in requiring additional formulations as well as safety data it is unlikely that such data will be presented, particularly for older products that have been in use since the 1960s.

The Neonatal and Paediatric Pharmacists Group together with the Medicines for Children Research Network is encouraging research into stable and palatable formulations of commonly used paediatric medicines. However, their top 20 list contains no medicines for oncology.

For children in the UK who are treated in oncology clinical trials, sourcing an appropriate formulation is difficult. Licensed formulations will invariably be suitable for adult-sized incremental doses, and alternative formulations are often only available as “specials”. Ensuring that the clinical trial supply meets the more detailed manufacturing and QC standards of the EU clinical trials directive is an additional difficulty in sourcing supplies for multicentre trials. A wide geographical distribution of patients in such trials run by academic sponsors, without the financial backing of the pharmaceutical industry, makes sourcing products more difficult and expensive than using “specials”. Excessive costs make NHS trusts less willing to participate. Conversely, manufacturing standards for clinical trials actually ensures a quality above that required for “specials” as a full manufacturer’s dossier must be submitted to the MHLRA before a clinical trials authorisation is granted. This includes details of the manufacturing process, containers, stability and QC, such as would be needed as part of an application to license a product.

Despite the incentives on market exclusivity that can now be granted to “orphan” products with a small market potential, it is unlikely that it will be commercially viable for even small scale pharmaceutical manufacturers to apply for marketing authorisation of many of these “specials”. It is expected that only drugs such as methotrexate and mercaptopurine, used for leukaemia as well as auto-immune conditions, would be commercially viable. Leukaemia is the most common childhood cancer (approximately 420 new cases in the UK per annum) requiring use of these drugs for two to three years. Autoimmune disorders are treated until disease regression has minimally responded to therapy, which can take years.

This article reviews appropriate formulations for oral medicines used in paediatric oncology, relating to acceptability and health and safety issues. Because of health and safety issues in handling chemotherapy in the home, cytotoxic medicines for children would ideally be in a form that requires minimal handling, has small dose increments and no risk of spillage. This reduces the risk of contamination of food, work surfaces and utensils that are used by other family members.

Current “special” products available in the UK for this patient group are then assessed for commercial viability as licensed products.

Review

Oral paediatric formulations that are, or are potentially, available for chemotherapy treatment in the UK were reviewed by formulation type then by current product availability in August 2008.

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also states products’ maximum current shelf lives, although these differ between production units. This indicates which would be currently suitable only for “specials” production.

Discussion
From discussions with more than one manufacturer, it appears that a shelf life of under a year would not be commercially viable, or acceptable to the MHRA, for large scale production, marketing and distribution.

Varying expiry for the same drug is indicative of the lack of necessity for manufacturers to test the long-term stability or microbiological integrity of the product if it is produced as a supply for a single patient, ie, a “special”. However, some manufacturers batch produce products and have invested in additional stability work. They are unlikely to share this knowledge with market competitors to retain a commercial benefit.

In the past few years some “specials” manufacturers have worked with the Paediatric Oncology Pharmacists group to:

- Provide nationally agreed strengths of “special” liquid preparations
- To provide clinical trial supplies of tablets and capsules in smaller sizes than adult licensed formulations
- To provide clinical trial supplies of standard strength liquid formulations
- To develop new liquid formulations of adult licensed medicines

This has helped to increase the number of batch produced “specials” available in paediatric oncology.

A number of products will have shorter expiry dates for reasons of microbial or physical stability, where stability data cannot be reliably extrapolated from one manufacturer to another. Where products are inherently unstable in solution and can only have a short expiry, eg, busulphan and procarbazine, it is unlikely to be economically viable to make commercial batches without undertaking additional stability work. They are unlikely to share this knowledge with market competitors to retain a commercial benefit.

It remains to be seen if manufacturers apply- ered an inhibitor to licensing a paediatric formulation of a drug.

Estimation of use was determined on the basis of a suitable formulation being freely available and not restricted to clinical trial use. It does not include use for palliative or third line chemotherapy, since such treatment is at the discretion of individual prescribers and is not part of national guidelines. So, although it underestimates total data usage, it assumes that all children aged nine years or under would prefer a liquid formulation. Children under this age who can swallow tablets should counterbalance these estimates to some degree. This made the use of oral etoposide difficult to estimate because its use is palliative for a wide tumour base. However this is a product that could be useful for adults with swallowing difficulties.

From projected annual usage, licensing is only likely to be commercially viable for mercaptopurine and methotrexate preparations. These preparations would also have a market outside oncology for immunosuppressive use. The potential adult markets of other cytotoxic formulations and application of EMA exclusivity licences for “orphan” diseases may increase viability for formulations of imatinib, cyclophosphamide, etoposide and temozolomide, although manufacturers seem reluctant to put resources into this limited market, which it was not possible to estimate. It remains to be seen if manufacturers apply...

Panel 2: Available preparations, their shelf life and annual use

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Shelf life</th>
<th>Annual usage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Busulphan 1–4mg/ml suspension, 5mg/ml (+ 2mg/ml)</td>
<td>Up to 15 days</td>
<td>(Licensed IV product replacing suspension)</td>
</tr>
<tr>
<td>Busulfan 25mg capsules</td>
<td>One year</td>
<td>(Mainly adult use)</td>
</tr>
<tr>
<td>Cyclophosphamide suspension 25mg–100mg/5ml, 10mg/ml, 20mg/ml, 25mg/1.5ml</td>
<td>Up to 15 days</td>
<td>88,000mg/year</td>
</tr>
<tr>
<td>Cyclophosphamide 25mg tablets, 25mg capsules</td>
<td>Three months</td>
<td>1,700 capsules/year</td>
</tr>
<tr>
<td>Etoposide oral solution 0.1mg–20mg/ml</td>
<td>Up to one month</td>
<td>300,000mg/year (estimated)</td>
</tr>
<tr>
<td>Hydroxycarbamide suspension 250mg/5ml, 500mg/5ml</td>
<td>Four weeks</td>
<td></td>
</tr>
<tr>
<td>Hydroxycarbamide 250mg or 300mg capsules</td>
<td>Up to two years</td>
<td></td>
</tr>
<tr>
<td>Imatinib suspension/powders</td>
<td>586,600mg/year</td>
<td></td>
</tr>
<tr>
<td>Lomustine 10mg capsules</td>
<td>(US import)</td>
<td></td>
</tr>
<tr>
<td>Lomustine 90mg powder for suspending</td>
<td>14,200mg or 250 doses/year</td>
<td></td>
</tr>
<tr>
<td>Lomustine 5mg–25mg capsules</td>
<td>Seven days</td>
<td>(As above)</td>
</tr>
<tr>
<td>Lomustine suspension 30–80mg/20ml</td>
<td>Six months</td>
<td>(As above)</td>
</tr>
<tr>
<td>Mercaptopurine 10mg tablets</td>
<td>Three years</td>
<td>155,000 tablets and capsules/year</td>
</tr>
<tr>
<td>Mercaptopurine 10mg capsules</td>
<td>One year</td>
<td></td>
</tr>
<tr>
<td>Mercaptopurine 100mg/5ml suspension</td>
<td>Up to 12 months</td>
<td>630,500ml/year (including clinical trials, excluding non-malignancy)</td>
</tr>
<tr>
<td>Mercaptopurine 10mg–100mg/5ml</td>
<td>Up to 16 weeks</td>
<td>(As above)</td>
</tr>
<tr>
<td>Methotrexate 2.5mg–62.5mg/5ml</td>
<td>One month</td>
<td>483,800mg/year</td>
</tr>
<tr>
<td>*Temozolamide suspension 50mg/5ml</td>
<td>60 days</td>
<td>25,500ml/year</td>
</tr>
<tr>
<td>Tretinoin (ATRA) NG mixture 40mg/5ml</td>
<td>Up to eight days</td>
<td>800ml/year</td>
</tr>
</tbody>
</table>

* Included in the Pro-file database
Preregistration training explained

These questions and answers, prepared by Damian Day, head of education and quality assurance at the Royal Pharmaceutical Society, explain what is happening regarding preregistration training and the registration examination as the Society prepares to hand over its regulatory functions.

Will preregistration training run in 2010 and who will run it? Yes, preregistration training will run as normal in 2010. The Society will run it initially then it will transfer to the GPhC when it opens for business as the regulator. The transfer will be seamless: trainees will not have to reapply to be trainees, and tutors will not have to reapply to be tutors. All applications and records will be transferred from the Society to the GPhC.

When will the transfer take place? The date has not been set yet but, whenever it is, it will not affect preregistration training. The date will be announced as soon as it is known.

What changes will the GPhC make to preregistration training? None in the previous years?

Will there be a registration examination in 2010? Yes. Examinations will take place on 25 June 2010 and 24 September 2010. There will be a registration examination in future years too.

Will the format of the registration examination be the same as in previous years? Yes.

Will tutors still assess students? Yes — no. You can join the Society if you want to but it is not compulsory.

What of the British Pharmaceutical Students’ Association? The BPSA will continue to work closely with the Society. Trainees can still be members of the BPSA.

How much will preregistration training and the examination cost? That is for the GPhC to decide. It will set fees every year, as the Society does now.

References